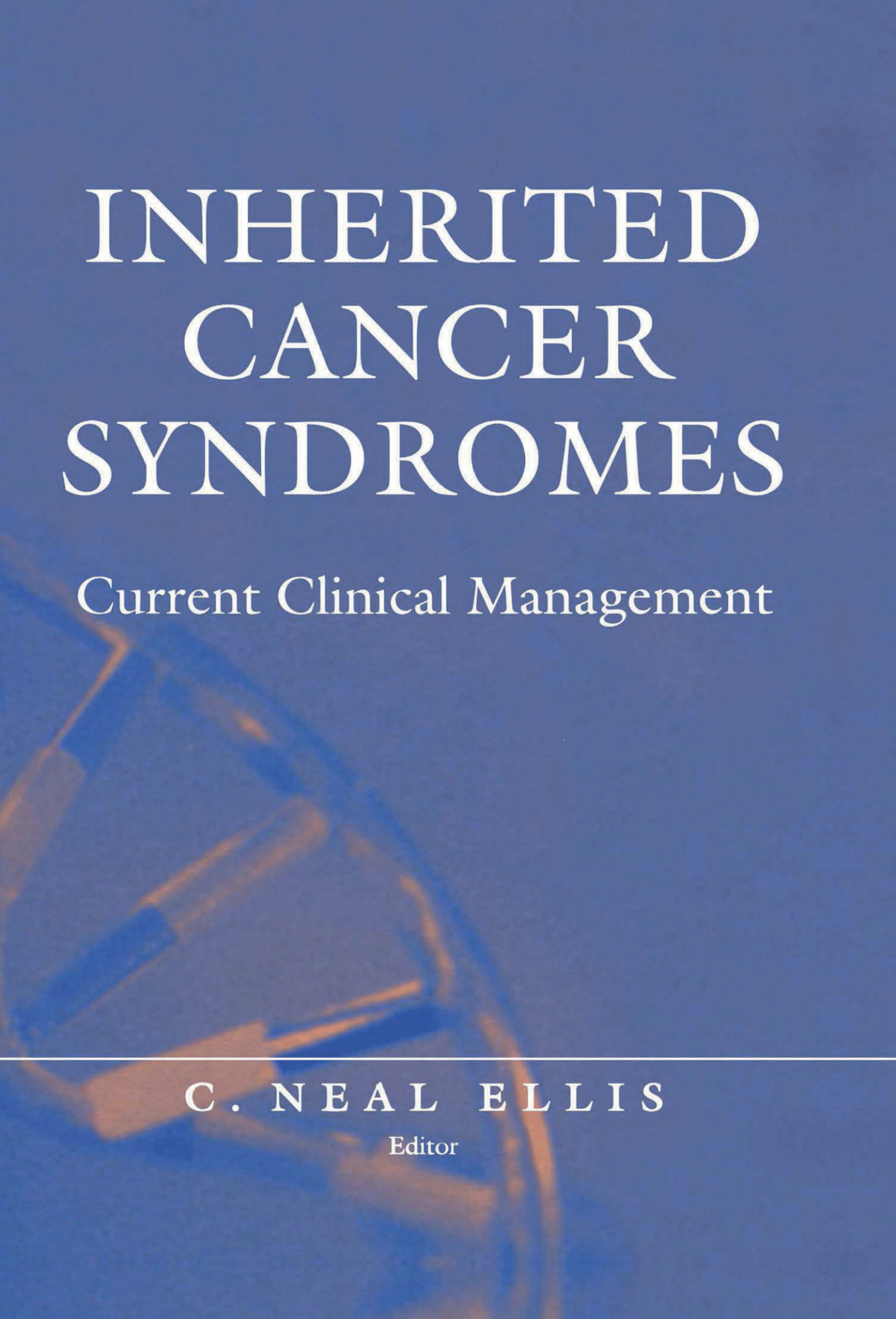
INHERITED CANCER SYNDROMES

Current Clinical Management



C. NEAL ELLIS

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Inherited Cancer Syndromes

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Preface

The goal in preparation of this text was to provide a source of information about the diagnosis, evaluation, and management of inherited cancer syndromes. Two decades ago, these syndromes were thought to be extremely rare, if they existed at all. Over the last 10 years, it has become apparent that 20% of patients with breast, colorectal, or gynecologic cancer will have a family history suggestive of one of these syndromes, and 5% will have the condition. The ramifications of having one of these diseases are significant for both the patient and their family, with a high risk of developing a malignancy in many organs at an early age.

Clinicians should be prepared to recognize and manage these diseases. This is not as simple as it sounds. While data derived from the technological advances in genetics can provide important information about the prognosis and possible manifestations of the disease, only in special circumstances can it be used to confirm or exclude the diagnosis. Instead, the diagnosis is made from the clinical information obtained by examination of a patient's family medical history. Despite the best efforts of the patient and their clinician the pedigree developed frequently has omissions and inaccuracies.

Another issue is the lack of consensus regarding the diagnostic criteria for these conditions. All of the currently accepted guidelines have been criticized, leaving the clinician confused as to who should be diagnosed with one of these syndromes. Avoidance of false-positive and -negative diagnosis is of particular importance given the implications of these diagnoses for patients and their families.

After the diagnosis is suspected or confirmed, the management of these diseases is also controversial. Treatment options can include aggressive cancer screening, preventive medications, and/or prophylactic surgery. There are few randomized, controlled trials showing the superiority of one strategy over another for patients with an inherited predisposition for cancer. Management of these patients is therefore based on clinical judgment, taking into account the clinical manifestations of these syndromes and the risks and limitations of the various therapeutic options.

It is hoped that this text will provide a source of information that is useful to the clinician in the recognition and management of these syndromes, and in the prevention of the suboptimal outcomes frequently associated with these diseases.

C. Neal Ellis, Jr., MD

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1

Assessing Genetic Risk of Cancer

Ronald T. Acton and Lisle M. Nabell

Our current understanding of the molecular pathophysiology of cancer explains many of the important epidemiology and clinical observations that have been made in the last 100 years. For example, the identification and characterization of genes responsible for hereditary cancer syndromes have explained the predisposition of members of affected families to develop site-specific cancer at a relatively young age.[1] A family history (FH) of site-specific cancer is now a leading risk factor for the subsequent development of breast, ovarian, colon, and prostate cancer and malignant melanoma.[1–6] The evolving understanding of the molecular basis of cancer has been based on the identification of several mutated genes that have been cloned and implicated in predisposing one to a variety of hereditary cancer syndromes.[7–17] This understanding has provided the ability to use genetic tests to estimate risk, predict onset, and aid in diagnosis and prognosis of many forms of cancer. However, the availability of genetic testing has created complex issues and controversies regarding their appropriate application, interpretation of test results, and implications for screening, preventive interventions, or corrective management decisions. Cancer control efforts to reduce the incidence of cancer have focused on prevention and early detection. These efforts will be most beneficial for individuals who are at highest risk. Thus, it is imperative that healthcare providers become familiar with the tools to assess a person's genetic risk of cancer, the general benefits and limitations of genetic testing in medical practice, and the process of making informed decisions about diagnosis and treatment of malignant disorders.

Excellent tutorials are available dealing with hereditary cancer syndromes.[18–20] Rather than provide an all-encompassing treatise, our goal in this chapter is to generate a practical guide to aid physicians in the assessment of the genetic risk of their patients for the development of cancer. The case scenarios presented are not intended to cover all familial or hereditary cancer syndromes but were selected as they illustrate the strengths and weaknesses of current cancer genetic knowledge. The information presented is aimed toward providing the basic

information a physician may need to identify those patients at high risk and determine the need for further assessment, enhanced screening, preventive intervention, or referral. Several guidelines have been published that should further aid physicians in incorporating genetic risk assessment into their practices.[8,21–31]

Collecting Family History of Cancer Information

The assessment of a patient for risk of cancer requires that the physician determine if one or more cancers are clustering in the patient's family and whether one is dealing with sporadic, familial, or inherited cases. This is complicated in that many cancers are prevalent. Thus, in a large family one might expect to see one or more cases of the more prevalent cancers. Familial clustering of cancer could be due to chance, common environmental exposures and lifestyle, or the inheritance of mutated genes. The challenge in assessing an FH is to determine which of these possibilities explain cancer in a family. For example, if one is dealing with a hereditary cancer syndrome for which a genetic test is available, then this tool can be utilized to refine the risk estimate. Thus, a mandatory step in identifying patients at high risk for familial cancer or hereditary cancer syndromes is to obtain a detailed FH of cancer.[32]

Many physicians do not obtain a sufficiently detailed FH of cancer information to identify a hereditary cancer syndrome. Moreover, it is common for healthcare providers to misinterpret or fail to act on the information provided.[33–38] Although patients are becoming more knowledgeable about their medical conditions, many will not present to their healthcare provider knowing whether they are a member of a family carrying a gene that predisposes them to cancer. It is the responsibility of the healthcare provider to identify the high-risk hereditary cancer syndrome patients.

The elements of a detailed FH of cancer are listed in Table 1.1. Many of the hereditary cancer syndromes include different types of cancers in the family, often affecting multiple generations. One of the hallmarks of hereditary cancer is early age of onset. A history of cancers that appear in family members under the age of 50 is an indication that one could be dealing with a hereditary cancer syndrome. Gleaning this information requires a structured approach to obtaining an FH of cancer information. While there are several venues in which the information can be obtained, it is our experience that the most complete and detailed information will not be obtained during an office visit to a

Table 1.1 Elements of a family history of cancer.

Include at least three generations
Include all cancers
Age of onset of each cancer
Age at death
Confirm diagnosis of affected individuals
Racial and ethnic background
Possible consanguinity

physician. Patients are often distracted by the reason for the visit and do not recall the detailed information requested. For this reason we recommend a two-step process.

During the office visit the physician or nurse should obtain a brief FH of disease and explain the need to obtain more detailed information on the disease of interest. There are several methods one can use to obtain this information.[39–41] One of the authors has developed and validated a Family History of Disease Assessment form on which a patient can record personal information.[39,42] This form queries the patient about the elements shown in Table 1.1 and provides a structured format on which to record the information. The form is mailed to the patient before or given to them during their office visit. This provides the patient the opportunity to contact family members and check medical or death records, which increases the completeness and accuracy of the information obtained.

The validity of the aforementioned approaches to collecting an FH of cancer information and the accuracy of the information reported by cancer patients appears good.[42–48] In one study, 83% of patients correctly identified the primary cancer site in their first-degree relatives.[43] The reporting site was accurate in 67% of second-degree relatives and 60% of third-degree relatives. False positives were 5%. In another study, the accuracy of cancer reported in first- and second-degree relatives was 91% and 74%, respectively.[44] A mistake in identifying the presence or site of the cancer was found in only 4% of first-degree and 15% of second-degree relatives. Although a small amount of overreporting by breast cancer patients of breast cancer in their families has been observed, the accuracy of reporting in first-degree relatives was >90%.[46] Accuracy improves when the reports of cases are confirmed by interviewing the purported affected members or obtaining medical records.[45,46] The sensitivity of self-reported positive history of colorectal cancer has been estimated in one study as 0.87 among cases and 0.82 among controls.[47] The specificity was estimated in both groups to be 0.97. The false-negative reporting has been observed to vary by tumor site and to be greater in individuals of nonwhite race and older age.[48] Other variables influencing false-negative reporting include time since cancer diagnosis, number of previous tumors, and type of treatment received.[48] The false-negative reporting rate for breast, colon, and prostate and bladder cancer was 20.8%, 42.1%, and 61.5%, respectively.

While it is recognized that the best estimate of an individual's cancer risk will depend on the accuracy and detail of the FH of cancer, there will be situations where confirmation of the information will not be feasible. Lack of confirmation could create a situation where the physician is apprehensive about recommending genetic testing or some of the more invasive preventive interventions.

Assessing Family History of Cancer Information

The next step in the process of a cancer genetic risk assessment is to use the FH of cancer information to construct a pedigree. Although one

can handdraw the pedigree, there are several commercially available[49,50] software programs and some in the public domain to aid in this process.[51,52] The pedigree should include all cancers, ages of diagnosis, and ages at death. We have also found it useful to send the constructed pedigree back to the patient, asking them to confirm the accuracy of the information. This also provides an opportunity to inquire about missing information. A letter is included informing the patient again of the importance of this process and including instructions to make any corrections or additions on the pedigree and return the pedigree in the self-addressed return envelope provided. Over 85% of pedigrees we generate come back with corrections or additions. These changes are indicative that the visual aspect of the pedigree, the queries, or the additional time to think about their family history stimulates patients to refine the information. The detailed FH of cancer information obtained can now be used to assess a patient's risk of cancer and determine if the pedigree suggests a hereditary cancer syndrome for which a genetic test is available that may help refine the risk estimate.

Table 1.2 lists a number of hereditary cancer syndromes for which the mutated gene(s) have been identified and genetic tests are available to identify these mutations. The Website www.genetests@genetests.org is a convenient source for (1) laboratories that perform various genetic tests and (2) clinics that specializes in genetic evaluation of patients and reviews of various genetic disorders. Using a select number of case scenarios, examples of how an FH of cancer information can be used to estimate a patient's risk of cancer, diagnose a hereditary cancer syndrome, and possibly refine the genetic risk through genetic testing will now be presented.

Familial Cancer That Does Not Fit the Criteria of a Hereditary Breast/Ovarian Cancer Syndrome

A pedigree analysis of an individual with a large family will often reveal one of the more prevalent cancers, e.g., breast or colon. However, the pattern of cancer may not fit the criteria for a hereditary cancer syndrome and may reflect the presence of sporadic cancer. Approximately 7% of breast cancer and 10% of ovarian cancer cases are estimated to fit an autosomal dominant pattern of inheritance.[53] Thus, a pedigree analysis is the only method, outside of widespread genetic testing of a population, to determine individuals who may be at high risk for cancer and would benefit from mutation testing.

Figure 1.1 is a pedigree in which the family has a positive history of breast cancer but the pattern does not meet any of the hereditary cancer syndrome criteria. The proband (IV: 1) is a 41-year-old white female who was referred to our familial cancer clinic due to the presence of breast cancer in her mother (III: 2) and maternal aunt (III: 3). The proband's mother had developed basal cell carcinoma at age 38 and unilateral breast cancer at age 36. The maternal aunt had developed breast cancer at age 62, and a maternal great aunt (II: 3) developed

Table 1.2 Hereditary cancer syndromes for which genetic tests are available.

Syndrome	Associated malignancies	Mode of inheritance	Gene
Breast/ovarian	Breast, ovarian, prostate, pancreatic	Dominant	*BRCA1*, *BRCA2* *BRCA2*
Cowden	Breast, ovarian, follicular of thyroid, colon	Dominant	*PTEN*
Li-Fraumeni	Breast, brain, soft-tissue sarcomas, osteosarcomas, leukemia, adrenocortical carcinomas	Dominant	*p53*
Familial polyposis	Colon	Dominant	*APC*
HNPCC	Colon, endometrial, ovarian, kidney, ureter, stomach, biliary tract, brain, small intestine	Dominant	*MSH2*, *MLH1*
Muir-Torre	Colon, breast	Dominant	*MSH2*, *MLH1*
Peutz-Jeghers	GI, breast	Dominant	*STKII/LKBI*
Turcot	Polyposis, brain	Recessive	Unknown
Malignant melanoma	Malignant melanoma	Dominant	*CDKN2A*
MEN2A	Medullary thyroid, pheochromocytomas, parathyroid adenomas	Dominant	*RET*
MEN2B	Medullary thyroid, pheochromocytomas, mucosal neuromas	Dominant	*RET*
von Hippel-Lindau	Hemangioblastomas of retina and nervous system, pheochromocytomas, renal cell	Dominant	*VHL*
Neurofibromatous 1	Neurofibrosarcomas, pheochromocytomas, optic gliomas	Dominant	*NF1*
Neurofibromatous 2	Bilateral acoustic neuroma, other tumors of nervous system	Dominant	*NF2*
Retinoblastoma	Retinoblasta, osteosarcoma	Dominant	*RB1*
Wilms' tumor	Nephroblastoma, hepatoblastoma, rhabdomyosarcoma, neuroblastoma	Dominant	*WT1*
Ataxia telangiectasia	Leukemia, lymphoma, ovarian, gastric, brain, breast	Recessive	*ATM*

Source: Adapted with permission from Olopade and Cummings.[122]

colon cancer at age 78. The maternal grandfather (II: 1) developed lung cancer at age 52. He was reported to be a heavy smoker. The maternal grandfather's sister (II: 4) developed breast cancer at an unknown age, but it was believed to be above the age of 50. The proband's father (III: 2), who was also a heavy smoker, developed lung cancer at

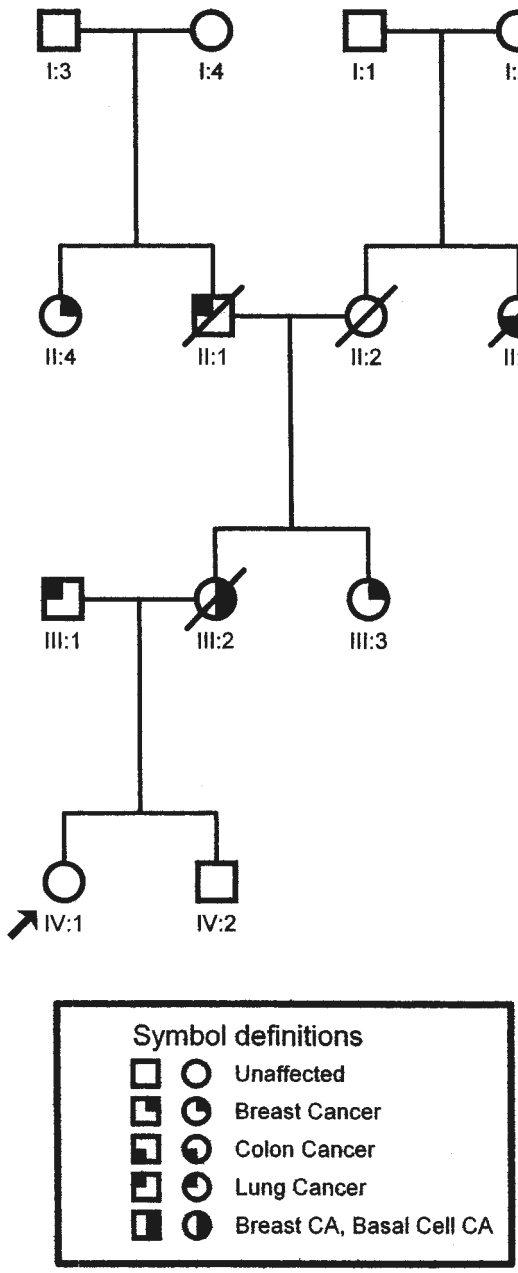

Figure 1.1 Example of a positive family history of breast cancer where the pattern does not meet any of the hereditary cancer syndrome criteria. *Note*: This and the other pedigrees that follow include only the relevant persons needed to assess the proband's risk of cancer.

age 65. The referring physician was probably alerted by the appearance of breast cancer in the proband's mother below the age of 50, which is one of the hallmarks of hereditary breast cancer, and breast cancer in her mother's sister. However, the pattern of cancer in this family does not strongly suggest hereditary breast cancer.

There are models one can use to estimate the proband's risk of breast cancer. The Gail model uses age, age at menarche, age at first live birth, number of prior breast biopsies, and number of first-degree relatives affected with breast cancer to calculate the probability that a woman will develop breast cancer at various ages in life.[54] The National Cancer Institute distributes a software version of this model, which is available at http://cancertrials.nci.nih.gov/forms/CtRisk-Disk.html. Another breast cancer risk assessment tool is the Claus model, which estimates risk based solely on the number of maternal and paternal first- and second-degree relatives and the age at which they developed breast cancer.[55] In the original publication a series of tables are provided that can be used to estimate risk based on various FH of cancer scenarios. A third model, the Bodian, can be used to estimate breast cancer risk for women in families where lobular neoplasia has been diagnosed.[56]

Each of these models provides a reasonable estimate of risk for breast cancer for most women but has its limitations.[57–59] The Gail model does not take into account FH of cancer. However, it has been reported to accurately assign a risk estimate for 87% of women.[59] The Gail and Claus models both fail to consider ovarian cancer risk, risk for women who have been diagnosed with lobular neoplasia, and the possibility of breast cancer predisposing gene mutations. The Gail model will overestimate the risk of women who do not carry a *BRCA* mutation and underestimate the risk in carriers of mutations.[60]

For the proband in Figure 1.1 the Gail model gave a lifetime probability of 19.9% that she would develop breast cancer compared to the population risk of 12.9%. This contrasts with the Claus model, which provided a probability of 29.6% that the proband would develop breast cancer by age 79.

Approximately 19% of women who develop breast cancer have a positive family history.[61,62] Of these, approximately 6% to 7% are due to mutations in either *BRCA1* or *BRCA2*.[63–65] One can determine the probability of *BRCA1* or *BRCA2* mutations occurring in a given family by use of the data obtained by Myriad Genetics Laboratories on 10,000 individuals who were referred to them for testing.[66] Myriad provides *BRCA1* and *BRCA2* mutation prevalence data in tabular form for individuals who did not report Ashkenazi Jewish ancestry and those who did at http://www.myriad.com/med/brac/mutptables.htm. Using these data the prevalence of deleterious mutations in *BRCA1* and *BRCA2* that have been observed in families with a history of cancer similar to the family in Figure 1.1 is 4.4%. This estimate is based on the observation that the proband has not presented with breast or ovarian cancer, that of the two relatives who presented with breast cancer, only one occurred below the age of 50, and that no history of ovarian cancer at any age had been observed in any relative at the time of analysis.

BRCAPRO is a family history model that uses Bayes theorem to calculate an individual's probability of developing breast cancer.[67] This model incorporates the probability that an individual carries a mutation in *BRCA1* or *BRCA2*. The software program CancerGene calcu-

lates breast cancer risks using Gail, Claus, BRCAPRO, and Bodian models and is available at no cost at http://www3.utsouthwestern.edu/cancergene.[68] The software also draws a pedigree and calculates *BRCA* gene mutation probabilities. BRCAPRO has been shown to be better in discriminating between *BRCA* gene mutation carriers vs *BRCA* gene mutation noncarriers than cancer risk counselors.[68] Using the BRCAPRO model to estimate risk for the proband in Figure 1.1 gave a risk of developing breast and ovarian cancer by age 86 of 12.3% and 1.8%, respectively. The probability that breast cancer in the proband's family was due to a *BRCA1* or *BRCA2* mutation using the BRCAPRO model was 2.2%, slightly less than the 4.4% derived from the Myriad tables.[66] The American Society of Clinical Oncology has recommended that *BRCA* genetic testing be considered for individuals whose family history of breast/ovarian cancer suggested an estimated prior probability of a *BRCA* mutation greater than 10%.[21] Additional guidelines have stipulated that testing should only be offered when the test can be adequately interpreted and the results will influence medical management. Thus, the probability that breast cancer in the proband's family in Fig 1.1 is due to a deleterious mutation in one of the breast cancer susceptibility genes is sufficiently low that testing for *BRCA* mutations is not indicated.

Figure 1.2 is the pedigree of a 39-year-old white female (III: 1) who was referred because her mother (II: 2) had developed ovarian cancer at age 49. The proband's maternal uncle (II: 3) had developed prostate cancer at age 48, and her maternal grandmother (I: 2) developed basal cell carcinoma at age 70. Her father (II: 1), a heavy smoker, developed lung cancer at age 65.

A woman with a first-degree relative who has developed ovarian cancer has a lifetime risk of 1 in 25 to 1 in 30 of developing ovarian cancer.[69] This compares to a risk of approximately 1 in 70 for a woman with no family history of ovarian cancer. The Gail model gave a lifetime risk of the proband developing breast cancer of 15.5% compared to the BRCAPRO model, which calculated a risk of 12.2% by age 89. Because there were no cases of breast cancer in the family, the Claus model could not be used. BRCAPRO also estimated a risk of the proband developing ovarian cancer by age 89 of 1.5%. The probability that cancer in this family is due to a *BRCA1* or *BRCA2* deleterious mutation was estimated as 1.1% and 6.2% by the BRCAPRO and Myriad models, respectively.

Familial Cancer That Fits the Criteria of a Hereditary Breast/Ovarian Cancer Syndrome

Figure 1.3 is a pedigree of a family where there is a high likelihood that cancer is due to deleterious *BRCA* mutations. The proband (III: 1) is a 43-year-old white female who developed breast cancer at age 43. Her mother (II: 2) and maternal grandmother (I: 2) had both developed ovarian cancer at ages 43 and 32, respectively. On the paternal side of the family an uncle (II: 4) had developed prostate cancer at age 74, and

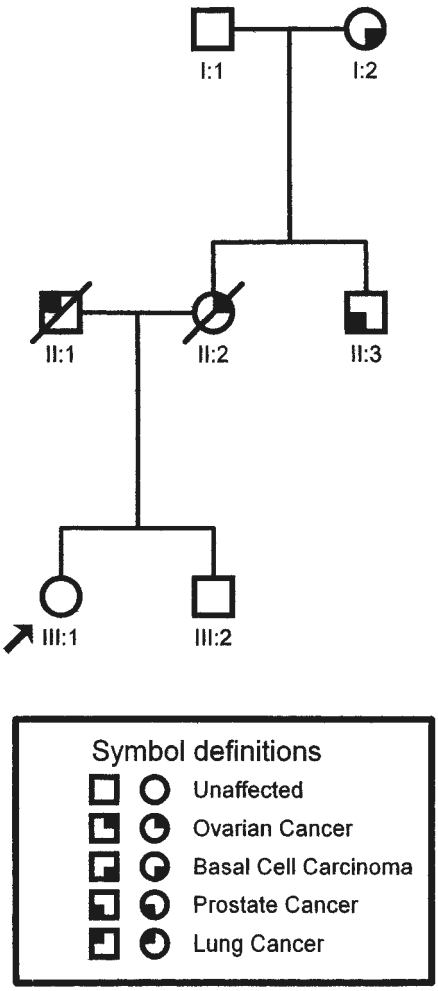

Figure 1.2 Proband referred based on a family history of ovarian cancer.

an aunt (II: 5) uterine cancer at age 40. The probability that cancer in this family is due to a deleterious *BRCA* mutation is 42.8% and 26.9% by the BRCAPRO and Myriad models, respectively. A comprehensive *BRCA1* and *BRCA2* gene sequence analysis of the proband did indeed reveal the germline *BRCA1* deleterious mutation E1250X. This mutation results in premature truncation of the *BRCA1* protein at amino acid position 1250. This information has important implications for the medical management of the proband. Mutations in *BRCA1* or *BRCA2* confer a 20% or 12% risk, respectively, that the proband will develop a second breast cancer within 5 years.[70–72] The proband's risk of developing a second breast cancer by age 70 years is 64% for *BRCA1*. Her lifetime risk of developing ovarian cancer due to a deleterious *BRCA1* mutation is ~44%.

It is important to remember that genetic information on a patient is different than other types of medical information. Genetic information

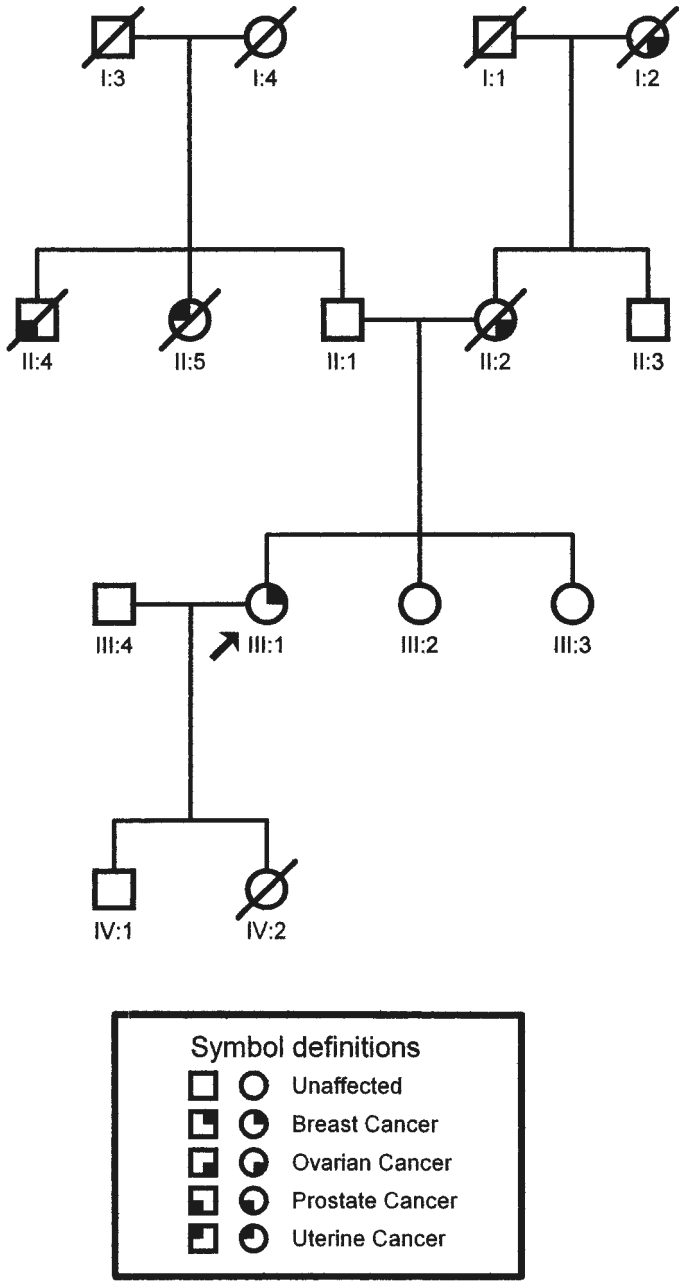

Figure 1.3 Proband presenting with breast cancer who was found upon testing to carry a deleterious *BRCA1* mutation.

impacts not only the patient receiving the assessment but also those family members who are still alive. Because deleterious *BRCA* mutations are inherited in an autosomal-dominant fashion, each of the proband's sisters (III: 2 and III: 3) and both children (IV: 1 and IV: 2) have a 50% chance of also having inherited the mutation. One can test the sisters for just the mutation observed in the proband rather than a

complete *BRCA1* and *BRCA2* sequence analysis because it is rare that a given family would possess two mutations. It is not recommended that a child be tested for an adult disorder until the age of medical consent.[73] However, each of the proband's children has a 50% chance of having inherited the mutation. If the daughter inherited the mutation, her risk of developing breast cancer by age 70 is 56% to 87%, and her risk of developing ovarian cancer approximately 44%.[65,74–77] This is significantly higher than the population risk of 7% for breast cancer and 1% for ovarian cancer by age 70. If the proband's son inherited the mutation, his risk would be increased to approximately 6% for male breast and possibly prostate cancer.[78]

There are families that have a high probability of possessing a deleterious *BRCA* mutation but on testing are found to possess a polymorphism that carries little or no risk. Figure 1.4 is the pedigree of a family that is in this situation. The proband (III: 1), a white female, presented with breast cancer at age 40. She had two sisters (III: 3 and III: 4), both of whom presented with breast cancer at the ages of 46 and 41, respectively. Her mother (II: 2) presented with bilateral breast cancer at ages 38 and 49. A maternal aunt (II: 3) had breast cancer, but the age of onset was unknown. Her maternal grandmother (I: 2) presented with ovarian cancer at around age 46. Based on the BRCAPRO model and the Myriad tables the probability that the family possesses a deleterious *BRCA* mutation was found to be 95.9% and 46.4%, respectively. However, the proband was found to possess the *BRCA1* variant R1347G, which results in the substitution of glycine for arginine at amino acid position 1347. Myriad reported that this variant had been observed in conjunction with separate protein-truncated mutations in *BRCA1* in an individual and in approximately 1% of controls of European ancestry.[79] The dilemma in counseling this patient is that one cannot predict if her risk for developing another breast cancer or ovarian cancer or the risk to her children is elevated over the risk estimate based on family history. This is a family where cancer may be due to the approximately 5% of mutated genes that are responsible for hereditary breast/ovarian cancer that have not been defined.

One of the features of hereditary breast/ovarian cancer is the presence of male breast cancer in a family. A male possessing mutations in *BRCA1* and *BRCA2* has an approximately 6% risk of developing breast cancer. Figure 1.5 is an example of a family with male breast cancer. The proband (III: 1) is a white female who presented with ovarian cancer at age 43. Her mother (II: 2) presented with breast cancer at age 62, and her maternal grandmother (I: 4) with ovarian cancer at age 82. A maternal aunt (II: 4) developed uterine cancer at age 26. On the paternal side her father (II: 1) developed breast cancer at age 62. A paternal uncle (II: 3) developed lung cancer at age 52, and her paternal grandfather (I: 1) developed pancreatic cancer at age 68. Several features of this family, e.g., ovarian/breast cancer on the maternal side and male breast and pancreatic cancer on the paternal side, suggest hereditary breast/ovarian cancer syndrome. The risk of pancreatic cancer is 2% to 3% by age 80 in a person carrying a *BRCA2* mutation.[80] The proband's risk of developing breast cancer by the age of 79 to lifetime

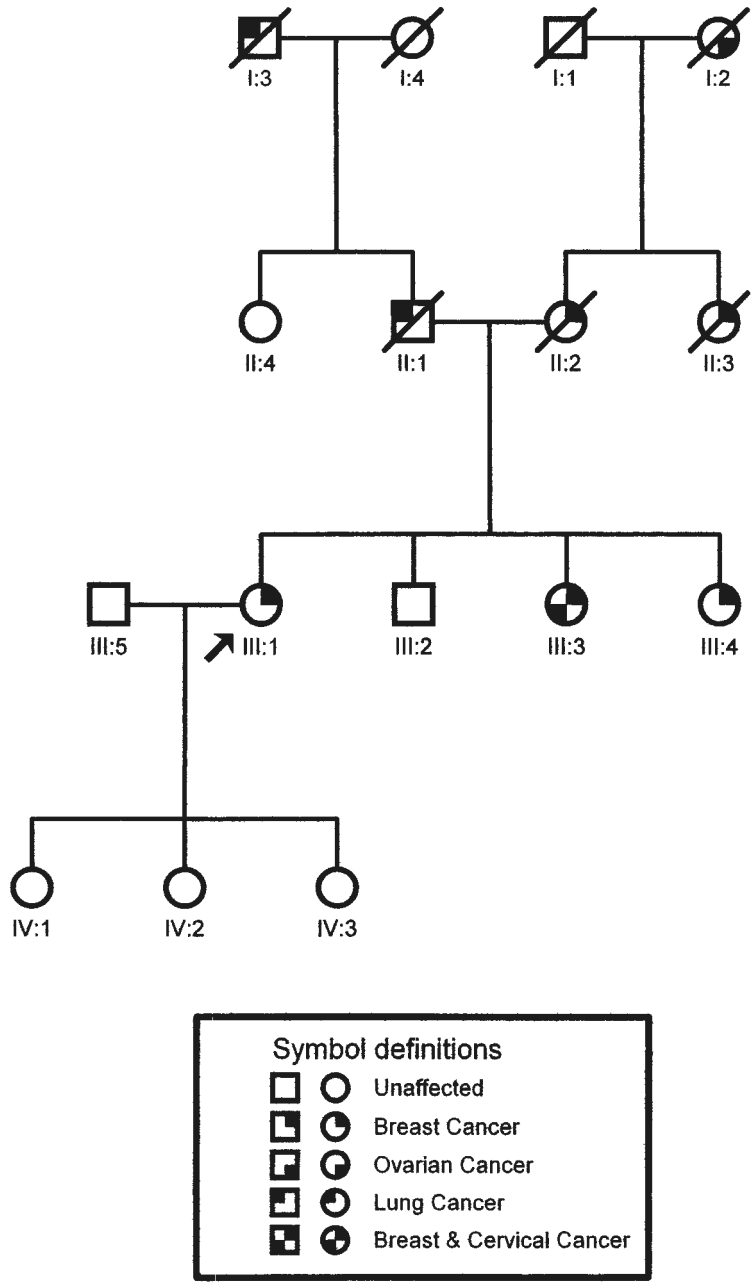

Figure 1.4 Proband presenting with breast cancer with a high probability of carrying a deleterious *BRCA1* mutation who was found to possess a variant of unknown clinical significance.

ranged from 9.6% to 34.3% using the Claus, Gail, and BRCAPRO models. The probability that cancer in this family is due to a deleterious *BRCA* mutation was estimated as 32.0% by the Myriad tables and 37.8% by the BRCAPRO model. Upon testing the proband was found to possess a Y105C variant, which results in the substitution of cysteine for

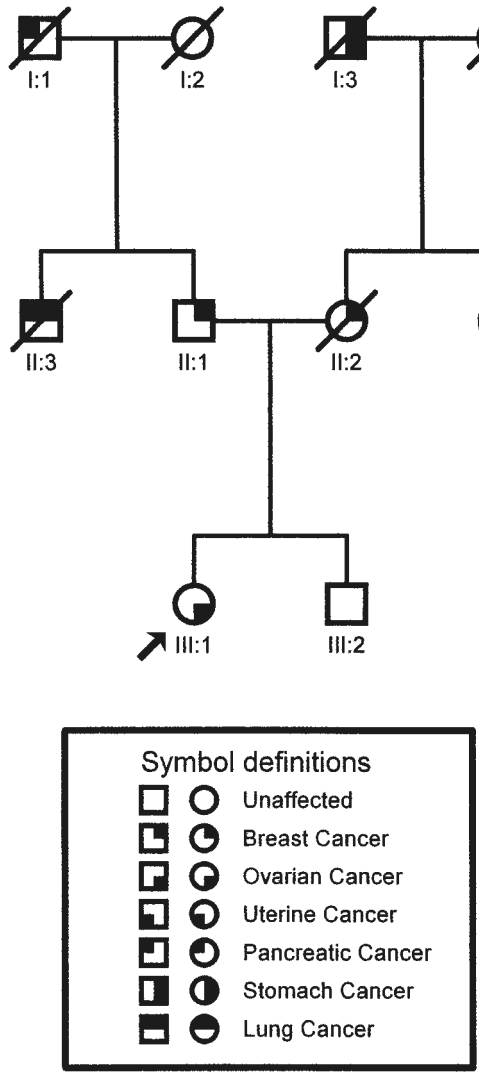

Figure 1.5 Example of a family with male breast cancer.

tyrosine at amino acid position 105 of the *BRCA1* protein. This variant may not affect the function of the protein and is probably not deleterious.

Figure 1.6 is the pedigree of a family where the proband (III: 1) presented with endometrial cancer at age 27 but had a significant family history of breast/ovarian cancer. One of the proband's sisters (III: 5) developed breast cancer at ages 48 and 53, and another sister (III: 6) developed bilateral breast cancer at age 40. The proband's mother (II: 2) was diagnosed with ovarian cancer at age 39 and breast cancer at age 62. Her maternal grandmother (I: 2) developed bilateral breast cancer at age 52. Her paternal grandmother (I: 4) had developed ovarian and cervical cancer, but age at onset was unknown. The pattern of cancer in this family certainly fits the criteria for hereditary

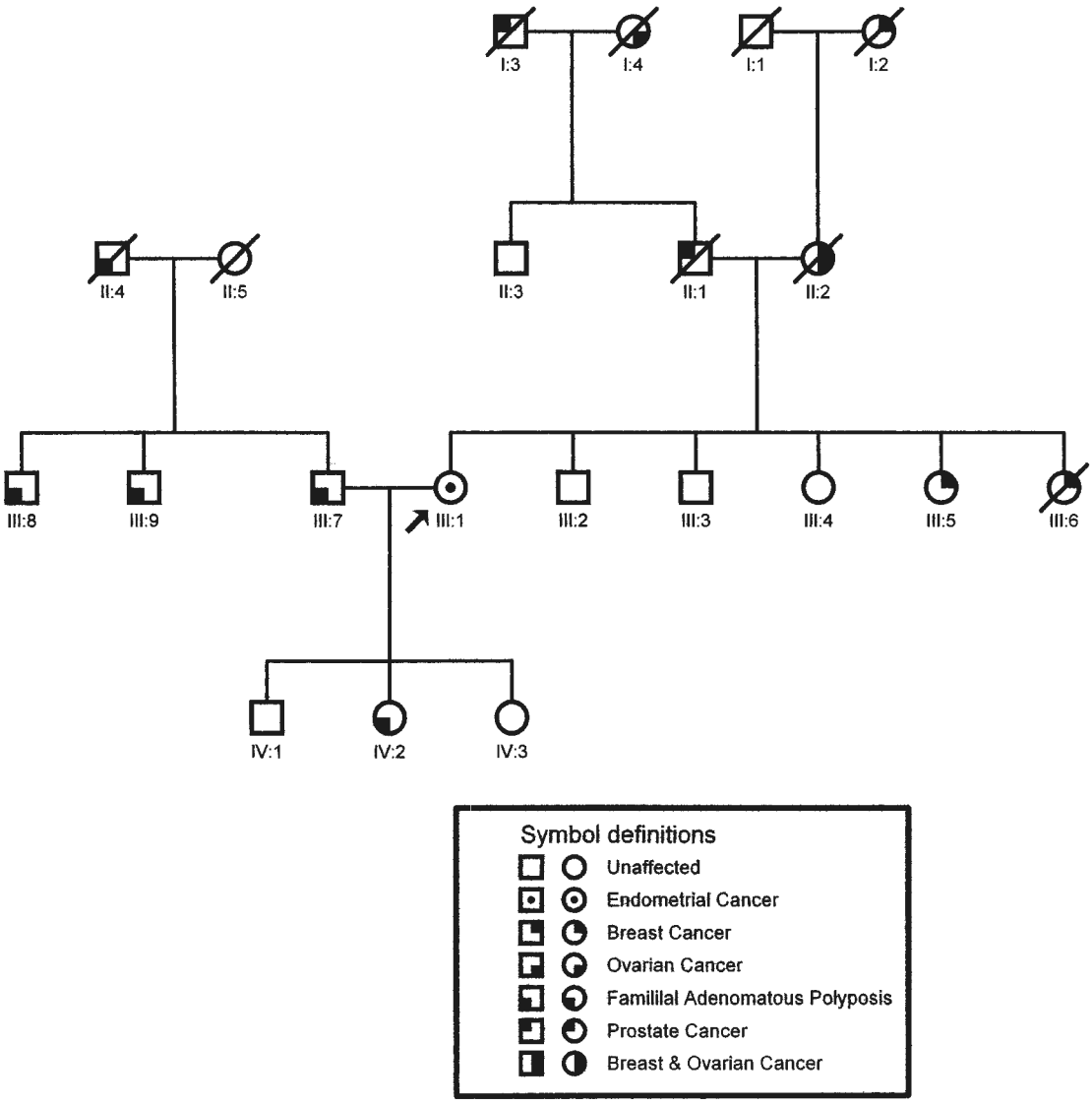

Figure 1.6 Proband whose family has a high probability of carrying a *BRCA* deleterious mutation that was negative upon testing.

breast/ovarian cancer syndrome, e.g., breast cancer onset below the age of 50, bilateral breast cancer, and ovarian cancer at any age. The probability of a deleterious *BRCA* mutation in this family was 16.5% by BRCAPRO and 16.4% by the Myriad tables. However, the proband did not possess a *BRCA1* or *BRCA2* deleterious mutation or variant. We have observed that approximately 15% of families that have a probability >10% of carrying a deleterious *BRCA* mutation are found on testing to either carry a variant of no known significance or to have a normal gene sequence.

The pattern of cancer in this family also illustrates that attention should be given to the entire family and not just those related to the

proband. The proband's spouse (III: 7) had developed familial adenomatous polyposis (FAP) at age 32. His two brothers (III: 8 and III: 9) also had been diagnosed with FAP as well as his father (II: 4), who succumbed to the disease. The proband and her spouse had one child (IV: 2) who had developed FAP at age 17. Familial adenomatous polyposis is inherited in an autosomal dominant fashion. Without knowing the mutation status of the adenomatous polyposis coli (*APC*) gene in the proband's spouse or her daughter, each of the other two children have a 50% chance of having inherited whatever the mutation might be. Adenomatous polyposis coli mutation carriers have an 87% risk of developing colon cancer by age 45.[81] Moreover, because 50% of *APC* mutation carriers develop adenomas by age 15 and 95% by age 35, it is appropriate to offer mutation testing to the 17-year-old child as well as her 23-year-old sibling.[28]

Ethnic Groups at Risk for Hereditary Breast/Ovarian Cancer Syndrome

Over 2% of individuals of Ashkenazi Jewish descent carry one of the following so-called "founder mutations":; 185delAG or 5382insC in *BRCA1* or 6174delT in *BRCA2*.[82–85] It has been suggested that Ashkenazi Jewish women consider testing for these mutations if they have developed early onset breast or ovarian cancer at any age regardless of their family history of cancer. Figure 1.7 is the pedigree of a family of Ashkenazi Jewish descent where six sisters had developed breast cancer. However, none of the sisters developed breast cancer before the age of 60. The proband (II: 1) was concerned about the risk to her daughter (III: 1) and therefore requested testing for the Ashkenazi Jewish panel of *BRCA1* and *BRCA2* mutations. The probability that breast cancer in this family was due to *BRCA* mutations based on the Myriad tables and BRCAPRO model was 3.2% and 77.2%, respectively. The proband did not test positive for any of these founder mutations. Other predisposing mutations have been reported in individuals of Ashkenazi Jewish descent.[86,87] A comprehensive *BRCA* analysis for this family is indicated.

Assessing Genetic Risk for Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of death by cancer in the United States. While approximately 75% to 80% of CRC is sporadic, it is estimated that 20% to 25% of cases are familial, and 5% of cases are due to FAP and hereditary nonpolyposis colorectal cancer (HNPCC).[15,28,88] A person with a first-degree relative who developed CRC has a 2% risk by age 50 and 7% by age 70 of developing CRC.[89] The risk estimate will vary depending on the affected relative (parents or sibling) and the site of the CRC. This risk estimate may be greater for a family with a hereditary CRC syndrome.[90] This can be emphasized by the following two familial cases of CRC.

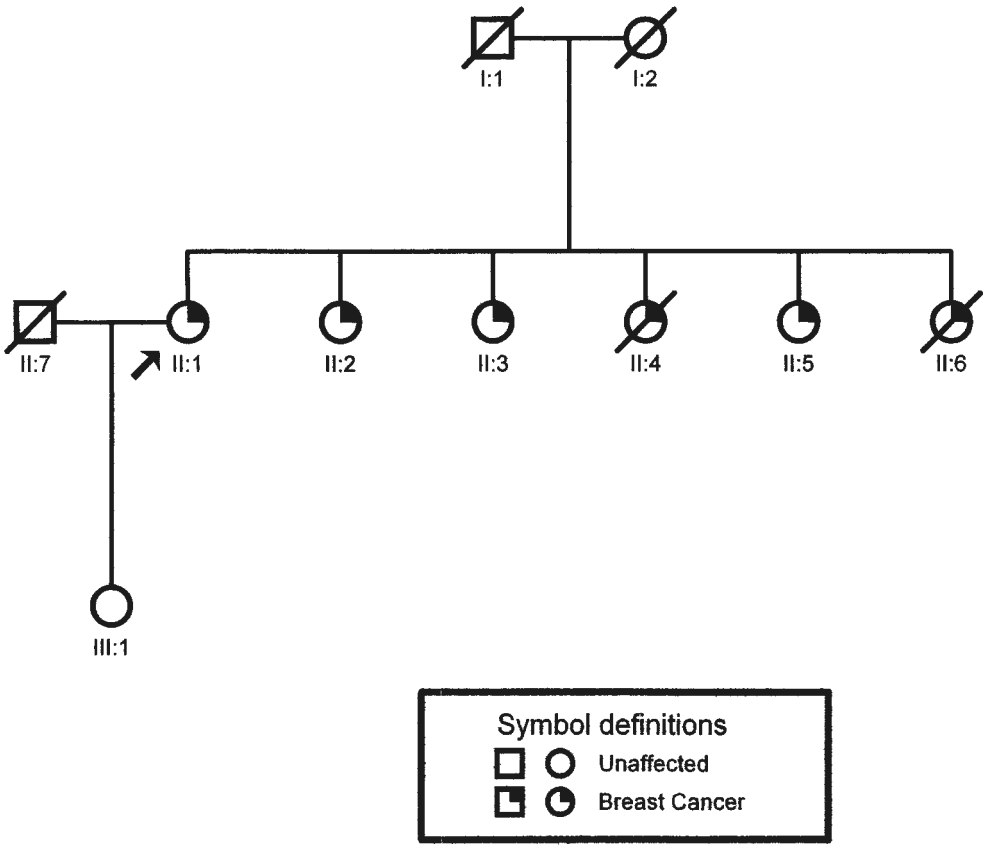

Figure 1.7 Ashkenazi Jewish family who did not possess the *BRCA* "founder mutations."

Figure 1.8 is the pedigree of a family with FAP. Familial adenomatous polyposis accounts for about 1% of CRC and is characterized by the hundreds to thousands of colonic adenomas that develop at an early age. Patients with FAP may also develop a variety of extracolonic manifestations, some of which are present in this family.[15] The proband (III: 1) is an African American female who was diagnosed with meduloblastoma and epidermoid cysts at ages 12 and 14, respectively. At age 15 she was diagnosed with desmoid tumors and FAP. Her mother (II: 2) was diagnosed with FAP at age 15 and succumbed to the disorder at age 33. She also had a history of recurrent intra-abdominal desmoid tumors. A maternal aunt (II: 3) was diagnosed with leukemia in her late 30s, which resulted in her death. The proband's grandfather (1: 1) was diagnosed with FAP at age 35 and died from the disorder at age 39. Familial adenomatous polyposis is caused by germline mutations in the *APC* gene.[91–93] Most of the over 300 mutations that have been reported result in truncation of the *APC* gene product.[94] The protein truncation assay[95] revealed that the proband in this family possessed a mutation in segment 2 of the *APC* gene product. The 16-year-old brother (III: 2) of the proband has a 50% chance of having inherited

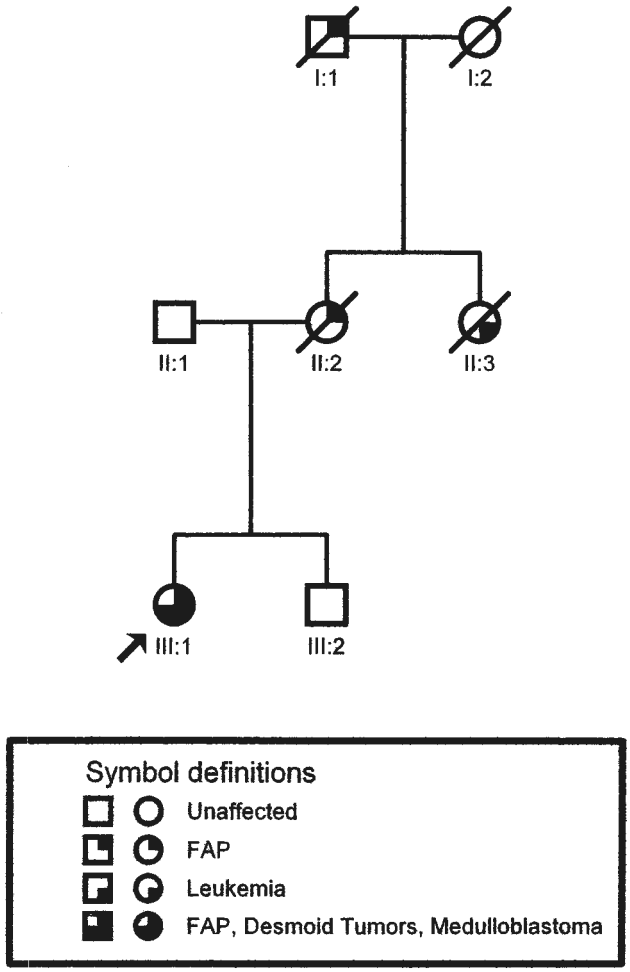

Figure 1.8 Family with FAP in three generations that tested positive for *APC* mutations.

this mutation. Because mutations in *APC* are highly penetrable the clinical manifestations of the disorder begin to appear by age 15. Testing of this individual (III: 2) is indicated.

In evaluating a patient for possible FAP one should be aware that certain mutations result in an attenuated form, others are more common among individuals of Ashkenazi Jewish descent, and some result in extracolonic manifestations.[15,96] Moreover, even among persons possessing the same *APC* genotype intra- and interfamilial phenotypic variability can occur. Adenomatous polyposis coli mutations have also been identified in families diagnosed with Turcot syndrome who manifest medulloblastoma.[90] These variables may make it difficult to distinguish FAP from other hereditary colorectal syndromes. A diagnostic strategy has been proposed to assist one in making the correct diagnosis.[97]

Hereditary nonpolyposis CRC is a hereditary cancer syndrome that requires a detailed FH of cancer information to diagnose the disorder and determine if family members would benefit from mutation testing. This is an autosomal-dominant inherited disorder that accounts for approximately 1% to 4% of all CRC. This syndrome has been defined by several criteria. The most stringent is the Amsterdam criteria, which requires three relatives, one of whom is a first-degree relative of the other two, diagnosed with CRC in two generations, with one or more cases diagnosed before the age of 50.[98] The Modified Amsterdam[99] and Amsterdam II[100] include cancer at several extracolonic sites. These include the endometrium, ovary, stomach, small bowel, hepatobiliary tract, pancreas, ureter, renal pelvis, and breast.[101,102] The Bethesda Guidelines are less stringent that the Amsterdam ones and emphasizes the patient's history of cancer.[103] The Bethesda Guidelines also were designed to help determine which patients should be tested for microsatellite instability (MSI).

Hereditary nonpolyposis CRC is due to mutations that occur in several mismatch repair (MMR) genes, although most testing is limited to *hMSH2* and *hMLH1*, where the majority of the HNPCC predisposing mutations occur.[104] It has been estimated that 1 of 10,000 individuals in Western countries carries a mutation in one of the MMR genes.[105] Of all the clinical criteria available, the Bethesda Guidelines have been reported as the most sensitive, but they are less specific than some tests for identifying patients with deleterious *MSH2* and *MLH1* mutations.[106] The sensitivity and cost-effectiveness is increased if one can screen the tumor of a family member for MSI.[107] Mutations in *MSH2* and *MLH1* are also found in Muir-Torre syndrome, a variant of HNPCC.[13]

Figure 1.9 is a pedigree of a family that meets the Amsterdam Criteria for HNPCC. The proband (III: 1) was a 38-year-old white female who was diagnosed with CRC at age 36. On the maternal side of her family the only reported cancer was leukemia in an aunt (II: 5) diagnosed at age 33. Her father (II: 1) was diagnosed with CRC at age 48, as was a paternal uncle (II: 6) at age 35. Her paternal grandmother (I: 4) was diagnosed with colon and breast cancer at ages 50 and 53, respectively. The BRCAPRO model estimated a probability of 56.2% that CRC in this family was due to a mutation in *MSH2* or *MLH1*. Testing the proband for mutations in these MMR genes revealed a G67R variant in *MLH1*. This variant results in the substitution of arginine for glycine at amino acid position 67 of the *MLH1* protein. The effect of this variant on the function of the *MLH1* protein is not yet known, and studies to date have not established its clinical significance. There could be mutations in the other MMR genes, which were not analyzed, that could result in the CRC observed in this family. This is another example where sequencing known genes currently available for testing did not define the cause of CRC. Although the siblings and child of the proband are at risk for CRC, based on the family history, their risk could be higher if it could be determined whether they carry a mutation. If an individual has developed CRC and carries a mutation in one of the MMR genes, he or she has a risk of developing another CRC or cancer in one of the extracolonic sites, which is a characteristic of HNPCC.

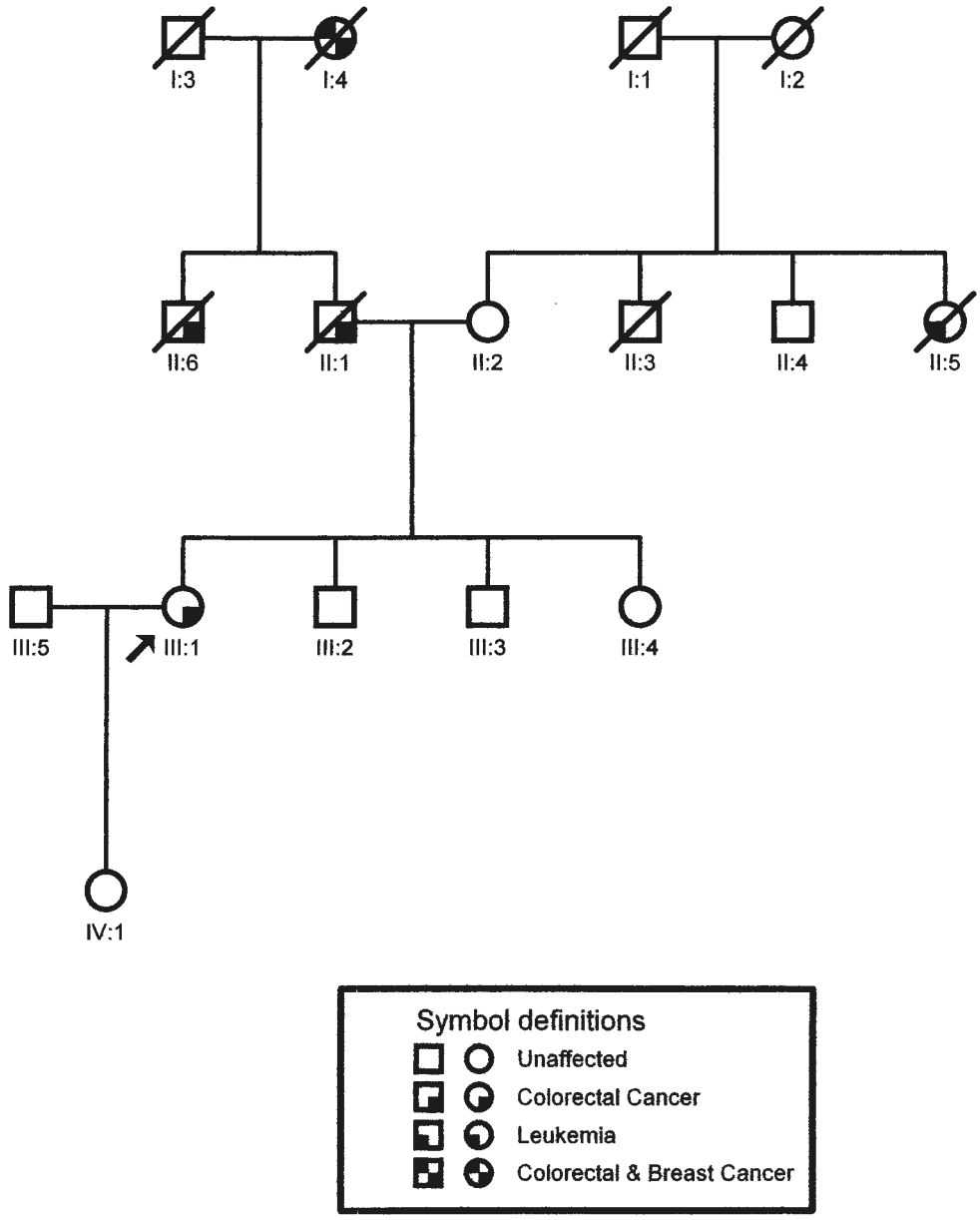

Figure 1.9 HNPCC family that meets the Amsterdam Criteria.

Assessing Genetic Risk for Melanoma

Cutaneous melanoma is one of the few cancers that have been increasing in incidence and mortality in the white population of the United States.[108] The average annual incidence rate during 1990 to 1997 was 15.3 for males and 10.2 for females per 100,000 people. This represented an annual percent change of 2.9 and 2.2 for males and females, respectively, during this time period. Lifestyle, sun exposure, fair skin,

light-colored eyes, poor ability to tan, Northern European or Celtic ethnicity, family history, benign nevi, and various major histocompatibility complex alleles have been reported as risk factors for cutaneous melanoma.[109–111] Approximately 8% to 12% of melanoma cases are thought to be familial. Mutations in *CDKN2A*, a tumor suppressor gene, are at present the most common cause of inherited susceptibility to cutaneous melanoma.[112,113] Mutations in this gene have been observed in approximately 40% of cutaneous melanoma families.[114–116]

Figure 1.10 is a pedigree of a family with multiple cases of cutaneous melanoma. The proband (II: 1) is a 46-year-old female who presented with melanoma at age 43. The proband is of Celtic ancestry and has a history of dysplastic nevi, many of which have developed into cutaneous melanoma. She has a brother (II: 2) and sister (II: 3) who presented with cutaneous melanoma at ages 44 and 18, respectively. A half-sister (II: 4) also developed cutaneous melanona in her early 40s.

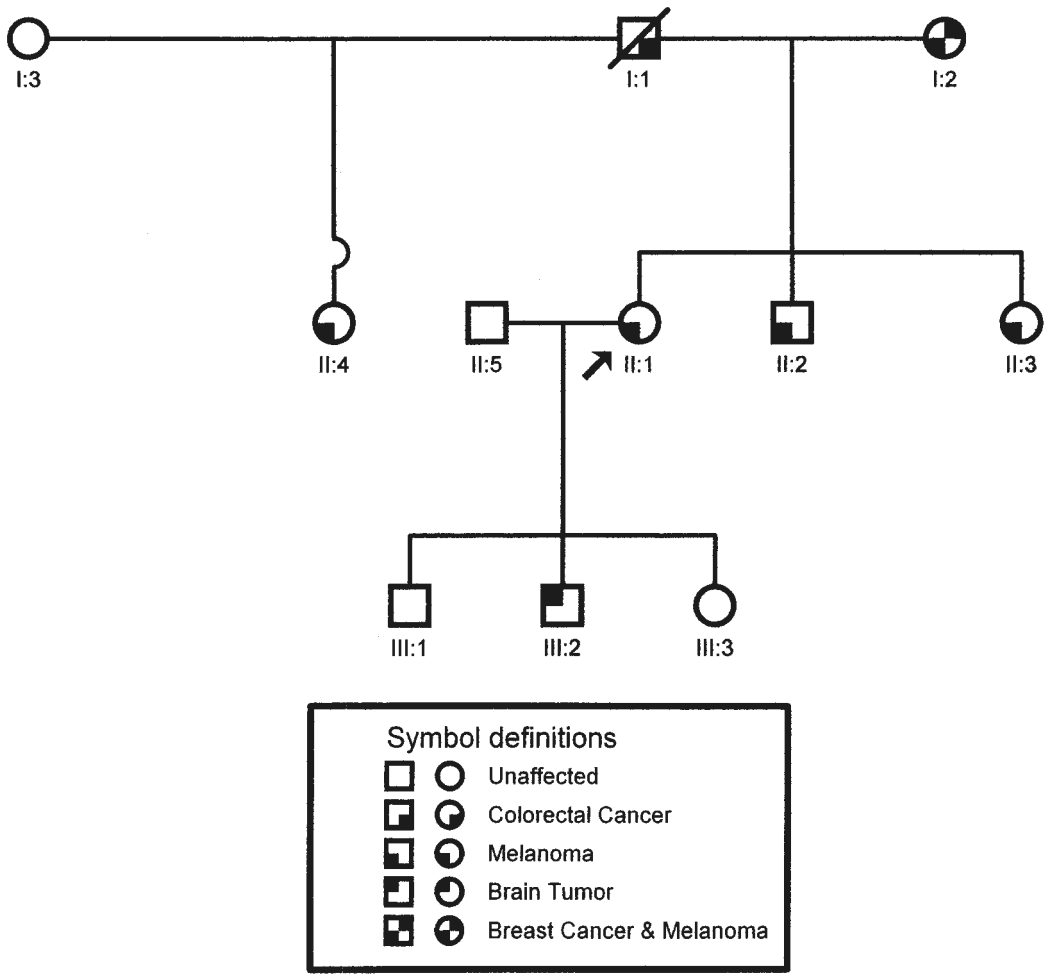

Figure 1.10 Familial melanoma family that tested negative for *CDKN2A*.

Her mother (I: 2) presented with cutaneous melanoma at age 41 and breast cancer at age 45. Her father (I: 1) was diagnosed with CRC at age 68. Genetic testing on the proband was conducted for germline coding mutations in exons 1 and 2 of the *CDKN2A* gene. No evidence was found for mutations in this segment of the gene. This family may represent one of those whose cutaneous melanoma is due to mutations in other exons of the *CDKN2A* gene, in noncoding regions, or in genes not yet defined.

Considering the Genetic Risk of Cancer for All Family Members

When assessing a person for his or her genetic risk of cancer one must be cognizant of all members of the family who may be at risk. Often, the person seeking the risk assessment will not be the member of the family at greatest risk. The pedigree shown in Figure 1.11 is an example. The proband (III: 1) is a 44-year-old white female who was referred due to the presence of cancer in her father (II: 1) and three of his siblings (II: 7, II: 8, and II: 9). As part of a cancer genetic risk assessment we ask the proband to obtain information on both the paternal as well as the maternal sides of their family. When the information was obtained on the family presented in Figure 1.11, and their pedigree constructed, three maternal first cousins (III: 4, III: 5, and III: 6) were reported as having presented with thyroid cancer at ages 43, 41, and 30, respectively. Given the history on the paternal side of the family the proband had a slightly increased risk of CRC based on a paternal aunt (II: 9) having developed CRC at age 50. However, the patient's greatest risk could possibly be for thyroid cancer. From 10% to 15% of all thyroid cancers are medullary thyroid carcinomas.[118] If the thyroid cancers in her cousins were medullary thyroid cancers, then with three members in a family being affected this would meet the criteria for familial medullary thyroid cancer.[117,118]

Familial medullary thyroid cancer can occur as a site-specific tumor or as one of the manifestations of multiple endocrine neoplasia (MEN) type 2A or 2B. These syndromes are associated with germline mutations of the *RET* proto-oncogene.[10] *MEN2A* is inherited as an autosomal dominant trait with high penetrance.[117] By age 70, 65% to 70% of individuals with *MEN2A* have developed one of the associated cancers. The vast majority of all cases of familial medullary thyroid cancer, *MEN2A* and *MEN2B*, have a mutation in the *RET* gene, with cases reporting as early as age 5 to 6.[117] The proband in Figure 1.11 was informed of the possibility of familial medullary thyroid cancer and instructed to communicate to her cousins their possible risk and the need to seek a genetic evaluation. Although the duty of the healthcare provider to inform other family members of their risk is unclear, there has been some litigation on this issue.[119,120] It seems prudent to at least discuss with the proband the estimated risk of other family members and ask that they contact them and strongly suggest they seek medical evaluation.

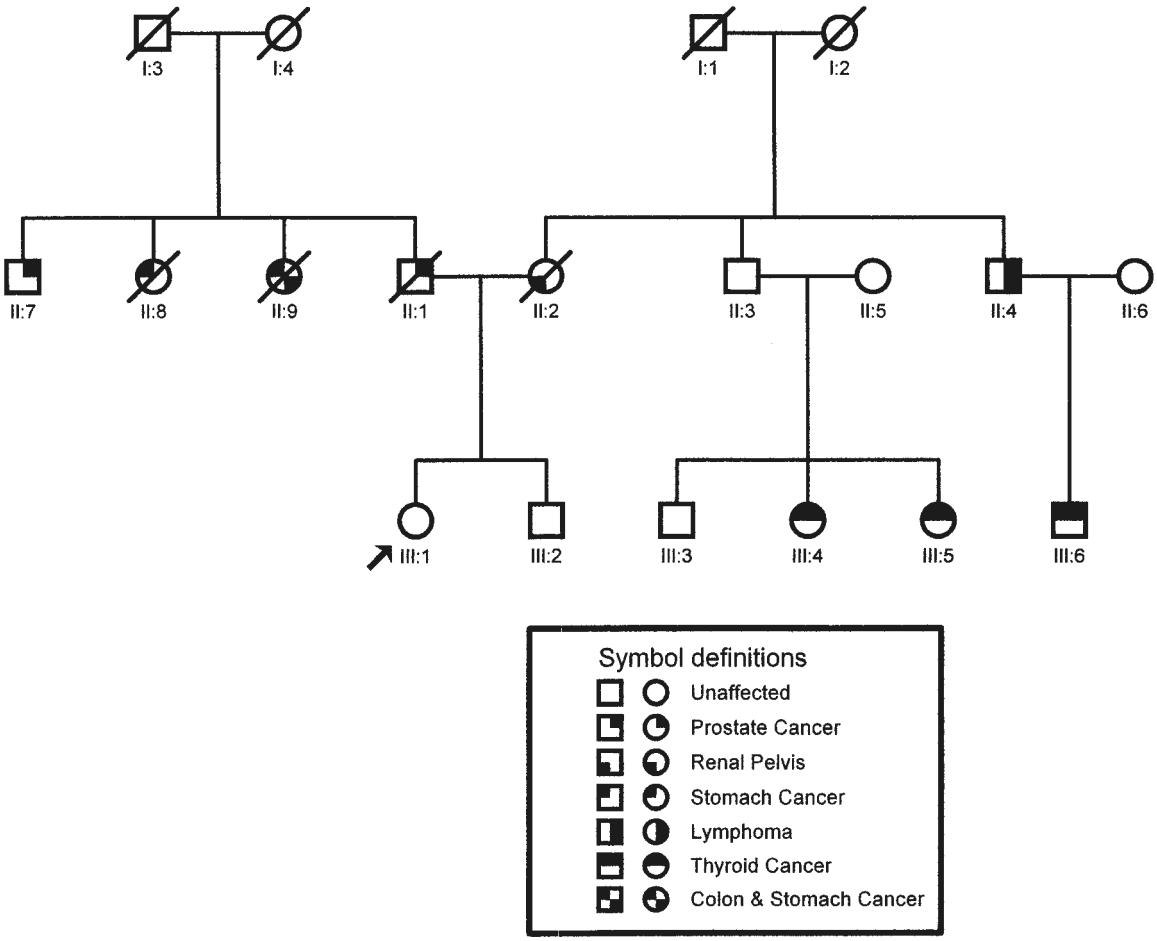

Figure 1.11 Family with familial thyroid cancer.

Conclusions

Assessing a patients' genetic risk is a complex undertaking. As summarized in Table 1.3 assessing cancer genetic risk is a multistep process that intimately involves the patient in obtaining information of their family. After a FH of cancer information is obtained and a risk estimate is generated, genetic counseling is recommended by several societies and required by several third-party carriers if genetic testing should subsequently be ordered. The counseling session should not

Table 1.3 Process of cancer genetic risk assessment.

Obtain family history of disease information	Assess cancer risk
Confirm family history of disease information	Conduct genetic counseling
Construct a pedigree	Genetic testing if indicated
Proband confirms pedigree	Postgenetic test counseling
	Preventive interventions
	Follow-up

only cover the genetic features of the disorder and the estimated risk for the proband and other family members but should also cover the appropriate cancer screening programs and preventive interventions that might be considered. In some cases, e.g., FAP and medullary thyroid cancer, it is imperative that genetic testing be undertaken. It should be recognized by the healthcare provider that one's FH of disease is not static. Therefore, the proband should be informed that his or her risk and the risk of family members might change should additional cases of cancer appear in the family. There should also be available medical specialists that the patient can be referred to should cancer screening and/or preventative interventions be indicated.

As was illustrated by several of the cases presented, there is still a void in our knowledge of hereditary cancer. However, the knowledge is increasing exponentially. In the future healthcare providers will have the tools to more accurately predict and presymptomatically diagnose cancer. The expectation is that this ability will lead to prevention of more cancer or a higher cure rate. As new information on the genetics of cancer becomes available, the issue arises as to the duty of the healthcare provider to recontact their patients. It has been suggested that at present a duty to recontact patients does not exists; it would raise substantial legal and ethical arguments, and the risk–benefit of such action is not clear.[121] However, the power of genetic information is becoming so great that this issue will most certainly receive greater attention in the future. The genetic revolution has captured the imagination of the public. More and more patients are becoming aware of their family history of disease and asking their physician about the impact of this information on their health. Thus, healthcare providers are being increasingly challenged by their patients to stay abreast of these advances.

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2

Genetic Counseling for Inherited Cancer Syndromes

Jill M. Yelland

"Once again society turns to genetic counselors to do what they do best—to guide us through the human aspects of the dilemmas genetic knowledge brings."[1]—Judy Garber, MD, MPH, Director, Cancer Risk and Prevention Program, Dana Farber Cancer Institute

While all cancers are genetic, only a fraction are part of a hereditary disorder. This small yet significant percentage of inherited cancers represent a disease of families—not individuals—whose members are at an increased risk for developing cancer due to genetic alterations passed through the germline. Genetic counseling is an integral service that should be provided to each patient or family with a known or suspected inherited cancer. The role of the genetic counselor in the medical evaluation and management of high-risk cancer patients is vast—from uncovering and analyzing the family medical history, to patient education, to identifying and interpreting genetic tests, to enlisting the patient in clinical trials and support groups, all while guiding the patient through powerful emotional responses to each of these steps. By participating in the genetic counseling process, patients receive information that may drastically influence their cancer screening and management plan, as well as their risk perception and quality of life.[2] The medical and psychosocial benefits from genetic counseling may extend beyond the patient to include relatives who may have otherwise remained anonymous within the healthcare system.

Many medical centers employ specially trained genetic counselors, or at the least a well-designed family history questionnaire, to assist in the identification of patients who are at risk for inherited cancers. Once a high-risk patient or family is identified, the genetic evaluation and counseling process should begin. During this time, the cancer genetic counselor assumes the primary role in patient education about cancer genetics, inheritance, genetic testing, and heightened surveillance programs. The genetic counselor also identifies and interprets genetic test results and provides referrals to support groups and specialists while addressing any psychological issues than may arise. A general outline of the genetic counseling process is presented in Figure 2.1.

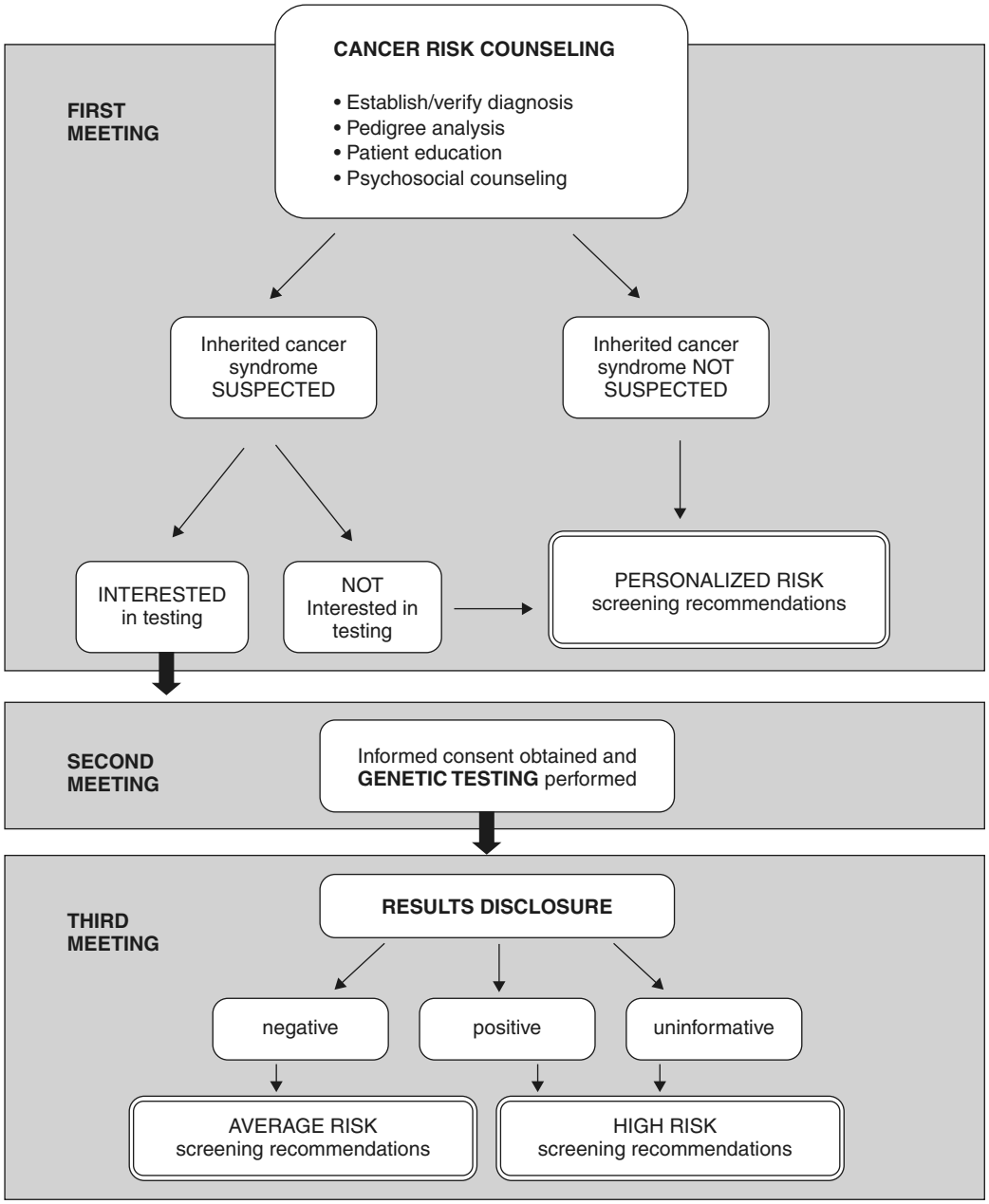


Figure 2.1 Flow diagram illustrating the process of genetic counseling. Cancer risk counseling usually occurs during the first visit, with a second visit required for genetic testing. Results and screening recommendations are discussed during a third face-to-face encounter.

Current Philosophy in Genetic Counseling

In 1947 geneticist Sheldon Reed at the University of Minnesota proposed the phrase "genetic counseling" to describe a process that had been practiced in multiple forms and with a variety of goals for

decades.[3] From eugenics to psychotherapy, the tenets of genetic counseling have evolved to reflect both scientific advances and social norms while incorporating the patient's core value system.[4]

Eugenics

The original form of what may be loosely classified as genetic counseling is known as eugenics. The first description of eugenics is credited to Francis Galton, a cousin of Charles Darwin, who proposed the establishment of social agencies aimed to "improve or impair racial qualities of future generations, either physically or mentally."[5,6] Eugenics referred to a social policy that purported to eliminate poverty, crime, and other socially undesirable situations while promoting intelligence and artistic ability. The eugenic movement was prominent in the late 19th and early 20th centuries and involved not only the scientific community but also many prestigious lawyers, politicians, and clergy. In the United States, eugenic ideas were widely accepted, and by 1926 nearly half of the 48 states had laws mandating that "mentally defective" individuals be sterilized.[4,6] The potential impact of eugenic ideology was not realized until the rise of Adolf Hitler and the Nazi party in Germany in the 1930s and 1940s. Under Hitler's reign, euthanasia for the "genetically defective" was legalized in 1939 and ultimately led to the deaths of more than 70,000 people with genetic disorders. This number is in addition to the Jews and many others killed during the Holocaust.[4,7]

Preventive Model

During the 1950s, the science of genetics and practice of genetic counseling focused on prevention rather than elimination as a means for social and community improvement. Central to this new preventive model was the study of disorders that follow predictable patterns within certain families. During this time, due to the lack of available diagnostic tests for genetic conditions, families were given information based on empirical risks and disease characteristics and in many cases simply encouraged to avoid childbearing.[4]

Client-Centered Model

In 1947, Reed proposed that genetic counseling should aim to benefit the *individual* or family rather than the community.[3] Scientific advances that occurred in both the biochemical and cytogenetic laboratories during the 1960s and 1970s expanded the options available for many genetic counseling patients, from amniocentesis and the identification of chromosomal aberrations in the fetus to adult carrier testing for a number of metabolic conditions.[8–13] The philosophy of genetic counseling expanded as well. During this time, genetic counselors strived to educate patients about disease, risks, and options, generally in a nondirective manner.

Nondirectiveness and client-centered therapy are counseling principles that were originally proposed in 1942 by renowned psychothera-

pist Carl Rogers.[14] Incoporating Rogers' principles into the process of genetic counseling serves to promote patient autonomy by shifting the role of decision-maker from the healthcare provider to the patient. In the client-centered model of genetic counseling, the patient is empowered to make decisions about genetic testing and disease management that are consonant with his or her needs, values, and life goals. Although not necessarily achieved (nor ideal) in every counseling situation, nondirectiveness has become a tenet of modern genetic counseling.

Current Philosophy

Although a primary expectation of most patients is to receive information during genetic counseling, it is often also necessary for the patient to deal with his or her emotional response before the information can be assimilated and acted upon.[15] Genetic counseling should therefore incorporate an exploration of the patient's family and social dynamics, as well as cognitive status and emotional needs. In this psychotherapeutic model of genetic counseling, the genetic counselor "must be able to recognize and elicit these factors, identify normal and pathological responses, reassure [patients] . . . that their reactions are normal, prepare them for new issues and emotions that may emerge in the future, and help them marshal intrinsic and extrinsic resources to promote coping and adjustment."[4]

In 1975 the American Society of Human Genetics offered a description of genetic counseling that is now widely referenced as the classic definition. Understanding the components of the *process* described, and the complexity of each, is critical for any physician or other healthcare provider who intends to provide genetic counseling to his or her patient.

Genetic counseling is a communication process which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder within a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to: (1) comprehend the medical facts including the diagnosis, probable course of the disorder, and available management, (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action which seems to them appropriate in view of their risk of recurrence, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.—American Society of Human Genetics[16]

Table 2.1 lists the seven primary goals of modern genetic counseling.

Genetic Counselors

The vast majority of genetic counselors are specially trained medical professionals who have obtained at least a master's degree from one of the approximately 24 accredited genetic counseling programs in the United States and abroad.[17] These graduate level programs provide di-

Table 2.1 Current principles of modern genetic philosophy.

Voluntary participation
Equal access by all populations
Public and patient education
Protection of privacy
Nondirective counseling
Psychological assessment
Confidentiality

dactic coursework as well as diverse clinical training experiences. Although most genetic counselors have graduated from specialized postgraduate training programs, nurses with additional training in genetics have also assumed the role of genetic counselor at some institutions. Genetic counselors provide a valuable contribution to the cancer clinic, having received training that prepares them to identify, collect, and analyze family history data and medical records, as well as perform risk assessments, and provide patient education and supportive counseling to families at risk for cancer.[18]

Genetic Counseling for Inherited Cancer

Most patients who participate in genetic counseling do so because a physician has referred them. A smaller but increasing number of patients contact the genetic counselor directly. Regardless of how the patient arrives for genetic counseling, his or her experience must be comprised of nine components. Listed in Table 2.2, each component should be addressed to ensure effective and thorough genetic counseling for every patient.

Collecting Medical Information

The family medical history is the key to the diagnosis of hereditary cancer.[19] A cancer patient who tells his oncologist or surgeon that cancer "runs" in his family and affects family members at strikingly early ages may learn about alternative forms of therapies, such as a chemoprevention trial for his healthy younger sister. Alternatively, a primary

Table 2.2 Key components of the cancer genetic counseling service.

Collecting medical information
Pedigree construction (three-generation minimum)
Establishing or verifying diagnosis
Risk assessment
Patient education
Genetic testing and informed consent
Results disclosure and interpretation
Risk management discussion
Psychological counseling

care or other physician who inquires about the family history of her healthy female patient may learn that she has a significantly increased risk for developing cancer because of the unusual number of relatives who have been affected by the disease at an unusually early age. Genetic counseling and subsequent testing may reveal that there is a familial cancer susceptibility mutation but that the patient does *not* carry the gene. Her risk is no higher than that of the general population and far less than what she had perceived her risk to be.

In some centers, comprehensive information about a patient's personal and family history information is gathered before the first appointment with the genetic counselor. At other centers, the genetic counselor may meet with the patient prior to receiving all of the information about his or her personal and family medical histories to first establish a face-to-face relationship with the patient. Centers may employ both methods, choosing which one to use depending on the needs of the patient.

To obtain and document information, patients should be provided with a questionnaire that asks detailed questions about personal and family medical history. For example, age at menarche, age at delivery of first child, and history of oral contraceptive use are examples of information that should be elicited from a female patient who is interested in her own risk for breast cancer. Type and site of primary cancer, age at diagnosis, and current age or age at death are all important pieces of information that should be asked about each affected family member when obtaining the family medical history. Table 2.3 outlines the basic elements of personal and family medical history that should be obtained for each patient.

A patient's true risk for cancer will remain hidden, and his or her well-being may be jeopardized if the family medical history is not adequately explored. Failing to identify high-risk patients or accurately analyze a family history may lead to inappropriate genetic testing, inaccurate interpretation of genetic test results, and inadequate screening recommendations.[19] The patient and other family members may also be deprived of therapeutic interventions that are reserved for the high-risk population or may remain unaware of the presence of a local support group of similar families.

Pedigree Construction

The next step in the process of a cancer genetic risk assessment is to use the family history of cancer information to construct a pedigree. The pedigree is a tool of paramount importance in the cancer genetics evaluation process. By providing a pictorial representation of the medical history of a family, the pedigree provides a basis for cancer risk analysis. A basic pedigree should represent an entire family, including at least three generations of all known maternal and paternal relatives. In 1995, Bennett et al. published standardized symbols to represent individual family members, relationships, and health status (Tables 2.4.1 and 2.4.2).[21]

Table 2.3 Components of a complete medical history.

Family history
At least three generations
Ethnic background
For affected individuals
Type and site of primary cancer
Age at diagnosis of each primary cancer
Treatment facility/location
Occupational/environmental exposures
Age at death/current age
Personal history
Date of birth
Cancer diagnosis information (if affected)
Site and type
Age at diagnosis
Current cancer screening methods
Type
Frequency
Results
Other medical conditions (e.g., ulcerative colitis)
Gynecologic history (female patients)
Age at menarche
Age at birth of first liveborn
Number of pregnancies
Hormone exposures
Dietary habits
Caffeine
Tobacco
Alcohol
Occupational exposures
Physical findings (congenital or skin defects)

Once the nuts and bolts of the pedigree are compiled and the family is represented pictorially, appropriate information should be recorded on the pedigree. The current age or date of birth of each relative should be recorded, regardless of whether or not the individual is affected with cancer or another disorder. The presence of healthy relatives who have reached an older age may have significant implications for the patient. For example, during Bayesian analysis (a risk assessment process described later in this chapter) certain healthy relatives may be taken into account and influence the risk assigned to the patient.

Important information about relatives who have been diagnosed with cancer should also be properly documented on the pedigree. While the pedigree symbols indicate the *type(s)* of cancer with which a relative has been diagnosed, the age at diagnosis should be recorded below the individual's symbol. Because inherited cancers tend to occur earlier in families than sporadic cancers, age of onset is a critical piece of information that must be obtained for each affected family member for accurate risk assessment for the patient. For patients who cannot recall or do not know the exact date of diagnosis or the age at which the relative was diagnosed, a rough estimate is acceptable. Knowing that a paternal aunt was in her 40s (and not her 80s) when she was diagnosed with colon cancer provides important information

Table 2.4.1 Common pedigree symbols, definitions, and abbreviations.

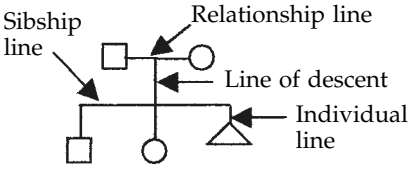
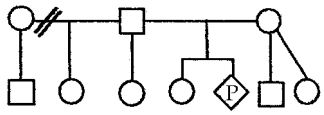
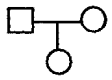
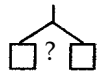
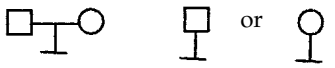
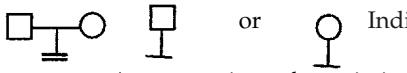
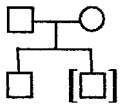
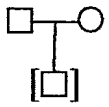
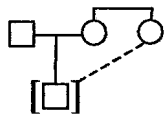
	Male	Female	Sex unknown
	b.1925	30 y	4 mo
Affected individual (define shading in key)			
Affected individual (more than one condition)			
Multiple individuals, number known	5	5	5
Multiple individuals, number unknown	n	n	n
Deceased individual	d. 35 y	d. 4 mo	
Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk
Pregnancy (P)	LMP: 7/1/9	P 20 wk	P
Spontaneous abortion (SAB); ectopic (ECT)	male	female	ECT
Affected SAB	male	female	16 wk
Termination of pregnancy (TOP)	male	female	
Affected TOP	male 16 wk	female	
Proband	P	P	P
Consultand			

Source: Adapted with permission from Bennett et al.[21]

about the potential for genetic susceptibility. Obtaining medical records on the individual in question may also clarify any uncertainties.

The physical and mental health status of the patient and each relative should also be recorded on the pedigree. Recurring conditions may be coded in the pedigree key, while less common illnesses are recorded

Table 2.4.2 Pedigree line definitions.

Definitions	Comments
Sibship line; Relationship line; Line of descent; Individual line 	If possible, male partner should be to left of female partner on relationship line Siblings should be listed from left to right in birth order (oldest to youngest) For pregnancies not carried to term (SABs and TOPs), the individual's line of descent is shortened
Relationship line (horizontal)	
a. Relationships 	A break in the relationship line (represented by slashes) indicates the relationship no longer exists Multiple previous partners do not need to be shown if they do not affect genetic assessment
b. Consanguinity	If degree of relationship is not obvious from pedigree, it should be stated (e.g., third cousins) above relationship line
Line of descent (vertical or diagonal)	
a. Genetic 	Biologic parents shown
Twins: Monozygotic Dizygotic Unknown 	A horizontal line between the symbols implies a relationship line
Family history not known/available for individual	
No children by choice or reason unknown  Vasectomy; tubal	Indicate reason, if known
Infertility  Azo-ospermia; endometriosis	Indicate reason, if known
b. Adoption In  Out  By relative 	Brackets are used for all adoptions. Social vs biologic parents denoted by broken and solid lines of descent, respectively

Source: Adapted with permission from Bennett et al.[21]

under the affected individual's symbol. Although the patient may just be seeking information about his or her cancer risks, other medical information learned may indicate an increased risk for other conditions. A woman who has a son with Klinefelter's syndrome (caused by the presence of an extra X chromosome in males) who learns that she carries a mutation in the *BRCA2* gene should be informed that her son has a furthered increase to his own risk to develop breast cancer. A

man who is concerned about the number of colon cancers on his mother's side of the family may also be at risk for early-onset Alzheimer's disease because of his older brother's recent diagnosis.

A questionnaire that asks specific questions about a patient's family history of cancer may be sent to the patient prior to the first appointment so that baseline analysis can begin. The pedigree can then be updated or modified during the appointment and as medical records are received.

Ethnic Background

Ethnic background is also an important piece of information that should be asked of each patient. Certain genetic conditions and mutations are more common in some ethnic populations. When assessing a woman's risk for hereditary breast cancer, the knowledge that she is of Ashkenazi Jewish descent influences her options for genetic testing as well as her predicted risks for developing breast or ovarian cancer. Three specific point mutations (185delAG or 5382insC in *BRCA1* or 6174delT in *BRCA2*) account for more than 90% of all inherited *BRCA1* and *BRCA2* mutations in the Ashkenazi Jewish population, with over 2% of individuals of Ashkenazi Jewish descent carrying one of these "founder mutations."[22–25] Ashkenazi Jewish women should consider testing for these mutations if they have developed early-onset breast cancer or ovarian cancer at any age, regardless of their family history of cancer. *BRCA* mutations are far more prevalent in women of Ashkenazi Jewish descent who are affected with ovarian cancer than in affected non-Ashkenazi Jewish women.[26] For individuals who carry one of these founder mutations, the risk for breast cancer is 45%, and the risk for ovarian cancer is 15%.[27]

Many genetic testing laboratories offer testing for the three Ashkenazi Jewish founder mutations on a single test panel at a cost far less than gene sequencing. Instead of full sequencing of the *BRCA1* and *BRCA2* genes, an Ashkenazi Jewish woman may opt for multisite testing. Of course, she should be properly educated about the benefits and limits of each test option before making her decision. If multisite testing is negative, the patient should be aware of the option of proceeding with full sequencing because as many as 1 of 10 Ashkenazi Jewish families with hereditary breast cancer may have a nonfounder mutation as the cause of their high cancer susceptibility.

In addition, the I1307K allele in the adenomatous polyposis coli (*APC*) gene appears to account for clusterings of colon cancer in some Ashkenazi Jewish families and may double the risk for colorectal cancer in Ashkenazim.[28–29] The I1307K allele was reported in 6.1% of all Ashkenazi Jewish individuals tested, in 10.4% of those affected with colorectal cancer, and in 28% of those affected with colorectal cancer in addition to having a positive family history.[28] These findings currently support the classification of the I1307K allele as a minor colorectal cancer susceptibility gene, but the lack of data regarding the clinical implications for carriers limits the utility of clinical genetic testing for this allele.[30]

Documentation

Once the pedigree is constructed, the names of the people who recorded and provided the information should be included somewhere in the pedigree. The date the information was obtained (such as the date of the patient's appointment) should also be documented. When new information is learned, the pedigree should be updated, and the date of the most recent modification or addition added.

Establishing or Verifying Diagnosis

Medical records should be obtained to establish or verify the cancer diagnoses within the family. Death certificates, pathology and autopsy reports, and office visit dictations are examples of the different types of information that may be gathered for this purpose. Although records may not be available for each affected family member, the efforts to obtain documentation of diagnoses may result in an interpretation of the family history that is drastically different from the history reported by the patient.

The importance of verifying diagnoses is demonstrated in Figure 2.2. In this example, the history reported by the patient is significant, but the information does not necessarily fit any of the known inherited cancer syndromes. However, once medical records were received, a different picture emerged, and the patient's risk for cancer was much clearer.

Physical Exam

A physical examination by a physician may also need to be performed to establish a diagnosis for a patient. For example, a physical exam and

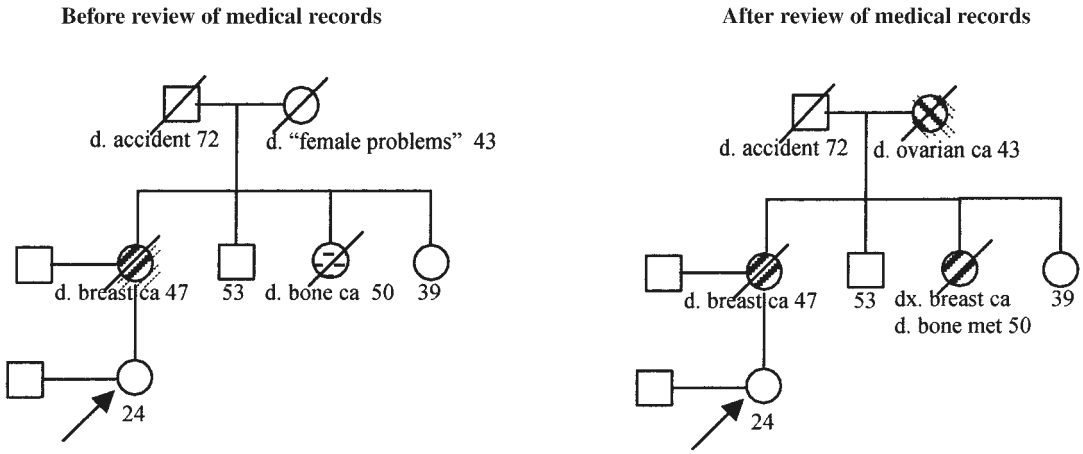


Figure 2.2 In the "before" pedigree (left), constructed from information obtained on a questionnaire, a 24-year-old patient reports an aunt with bone cancer and a grandmother who had "female problems." The "after" pedigree (right) reflects changes made after medical records were received on the affected family members. The new information learned from review of the medical records revealed that the patient's risk for breast and ovarian cancer is drastically increased. She is also identified as an appropriate candidate for genetic testing of the *BRCA1* and *BRCA2* genes based on this new information.

Table 2.5 Physical characteristics and mode of inheritance for selected cancer syndromes.

Syndrome	Primary cancer risks	Physical findings	Inheritance (*gene*)
Cowden's syndrome	Breast cancer, thyroid cancer	Facial and oral papules; macrocephaly	Autosomal dominant (*PTEN*)
FAP	Colon cancer	Multiple polyps; retinal pigmentation (CHRPE); desmoids tumors; sebaceous cysts; impacted teeth; osteomas	Autosomal dominant (*APC*)
Turcot syndrome	Colon cancer and brain tumors (medulloblastoma and glioblastoma)	Polyps; café-au-lait spots; sebaceous cysts on skin	Autosomal dominant (*APC*, *MLH1*, *MSH2*)
Muir-Torre syndrome	Colon cancer and skin cancers	Sebaceous adenomata; keratoacanthomata; basal cell carcinoma	Autosomal dominant (*MSH2*)
Peutz-Jeghers syndrome	Breast cancer and colon cancer	Pigmented spots on lips, perioral areas, buccal mucosa, and extremities	Autosomal dominant (*STK11*)
Multiple endocrine neoplasia, type 2B	Medullary thyroid carcinoma, pheochromocytoma	Enlarged, nodular lips marfanoid habitus	Autosomal dominant (*MEN2*)
Neurofibromatosis, Type 1	Neurofibroma, optic glioma	Café-au-lait spots, axillary freckling, macrocephaly, Lisch nodules, pseudoarthrosis	Autosomal dominant (*NF1*)

review of medical records may lead to a diagnosis of the rare Peutz-Jeghers syndrome in a patient with multiple colorectal polyps. Table 2.5 highlights the primary physical findings associated with selected inherited cancer syndromes.

Risk Assessment

Perhaps one of the most critical components of the genetic counseling process is risk assessment. Cancer risk assessment is influenced by four entities: the patient's knowledge of cancer genetics, the patient's psychosocial state, technologies currently available, and modern cancer management techniques.[31] The risk that is provided to the patient in turn influences decisions about postmenopausal hormone replacement therapy, the age at which to begin mammograms, the use of tamoxifen in breast cancer prevention, and surgical options such as mastectomy and oophorectomy.[32] Information obtained by interview, questionnaire, and medical records should be carefully reviewed for incorporation in the risk assessment process. The risk provided to a patient should be calculated based on the patient's family history and personal medical history. A number of risk models and calculation methods are described below.

Bayes Method

Bayesian analysis is used in risk assessment when additional information is available that may modify risks that are calculated using mendelian probabilities. Bayes theorem combines prior and conditional probabilities to provide joint and posterior probabilities of unknown and often mutually exclusive events. In other words, a patient's mendelian risk for cancer can be modified by mathematically accounting for cancer status, current age, and test results. Bayesian analysis may be used to determine the probability of being a gene carrier, the probability of a disease being present (in patient or offspring), and the probability of a disease being present if a test is positive (also known as the *positive predictive value* of a test). An example of Bayesian analysis is presented in Figure 2.3.[33]

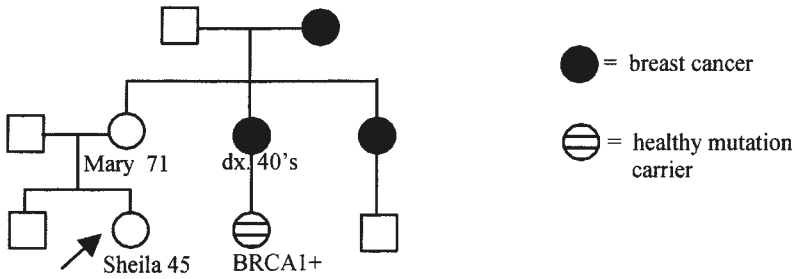
Breast Cancer Risk Models

Looking beyond the pedigree, additional patient and family history information may be incorporated into one of the available multidimensional risk assessment models when assessing the risk for breast cancer. The most widely used model is the Gail model, which is derived from the Breast Cancer Detection Demonstration Project (BCDDP).[34] The BCDDP was a large mammogram-based screening program conducted in the 1970s. Incorporating the number of affected family members, patient history of breast biopsy, age at menarche, and age at first live birth, the Gail model provides 5-year and lifetime risk estimation for breast cancer. These risk numbers are derived by obtaining and multiplying the relative risks from several categories in addition to family history, and then multiplying this product by a population risk to yield the patient's cancer risk at 5 years and over lifetime. An online version of the model can be found on the National Cancer Institute's website at http://bcra.nci.nih.gov/brc/.[35] Astra-Zeneca also supplies handheld units to quickly calculate a patient's risk using the Gail model.

The Claus model is the second of the two commonly used breast cancer risk prediction models.[36,37] The Claus model was derived from data obtained during the Cancer and Steroid Hormone (CASH) Study, a large case-control study of breast cancer patients. This model takes both paternal and maternal family histories into account by including first- and second-degree relatives of the patient. The risk numbers are also based on the assumed prevalence of high-penetrance genes for susceptibility to breast cancer at the time the CASH Study was completed. The Claus model provides the patient with a series of cancer risk predictions, one for each decade of life from age 29 to 79 (Table 2.6).[36]

These models are useful, although each has limitations that should be understood and explained to the patient whose risk is being calculated. The Gail model does not incorporate information about the patient's paternal relatives (such as a paternal aunt and cousin with breast cancer) and in general appears to underestimate the risk for younger women who are not undergoing routine screening by mammography. The Claus model ignores factors outside of family history. Neither model is appropriate for families with an identified genetic mutation

Sheila is a 45 year-old woman who calls a genetic counselor because she is concerned about her risk for breast cancer. She reports that her cousin has tested positive for a mutation in the BRCA1 gene. Sheila also informs the counselor that while her cousin's mother had breast cancer in her 40's, her own 71 year-old mother, Mary, is healthy. Two other family members also had breast cancer. The basic pedigree is shown below.



Sheila's risk based on Mendelian analysis is 25%. Mary's Mendelian risk is 50%. These risks, however, can be modified by the information Sheila was able to provide about her mother Mary as well as by her own health status.

First, because Mary has reached the age of 71 without developing breast cancer, the likelihood that she carries the familial mutation in the BRCA1 gene is reduced. Mary's posterior probability of carrying the BRCA1 mutation given that she is healthy [p(C/U)] is calculated using the following Bayesian equation:

$$\mathbf{p(C/U) = p(U/C)p(C) / [p(U/C)p(C)] + [p(U/NC)p(NC)}$$

where, **p(U/C)** = probability of being unaffected if a gene carrier
p(C) = probability of being a gene carrier
p(U/NC) = probability of being unaffected if not a gene carrier
p(NC) = probability of not being a gene carrier

Mary's risk can be mathematically modified since we know her current age and health status. At age 70, the risk for breast cancer in a known BRCA1 mutation carrier is 0.82. In other words, 18% of BRCA1 mutation carriers have *not* developed breast cancer by the age of 70. We also know that in the general population, only 7% of women will have developed breast cancer by age 70. Plugging our information into the Bayesian equation above, Mary's risk for carrying the BRCA1 mutation is modified from 50% to 16%:

$$\mathbf{p(C/U) = (.18)(.5) / [(.18)(.5)] + [(.93)(.5)] = .16 \text{ or } 16\%}$$

Sheila's risk can then also be adjusted using Bayesian analysis; her Bayesian risk for carrying the BRCA1 mutation is 6.8%. This is less than the originally predicted 25% Mendelian risk (or the 8% Mendelian risk based on Mary's Bayesian analysis.)

Figure 2.3 Case example using Bayesian analysis in assessing risk for breast cancer.

Table 2.6 Cumulative risk of breast cancer according to the Claus model.

No. of relatives with breast cancer and their age at diagnosis	Cumulative breast cancer risk according to age (%)				
	39 y	49 y	59 y	69 y	79 y
One first degree relative					
20–29 y	2.5	6.2	11.6	17.1	21.1
30–39 y	1.7	4.4	8.6	18.0	16.5
40–49 y	1.2	3.2	6.4	10.1	13.2
50–59 y	0.8	2.3	4.9	8.2	11.0
60–69 y	0.6	1.8	4.0	7.0	9.6
70–79 y	0.5	1.5	3.5	6.2	8.8
One second degree relative					
20–29 y	1.4	3.5	7.0	11.0	14.2
30–39 y	1.0	2.7	5.6	9.0	12.0
40–49 y	0.7	2.1	4.5	7.6	10.4
50–59 y	0.6	1.7	3.8	6.7	9.4
60–69 y	0.5	1.7	3.8	6.7	9.4
70–79 y	0.4	1.3	3.2	5.8	8.3
Two first degree relatives					
Younger age at diagnosis 20–29 y					
Older age at diagnosis					
20–29 y	6.9	16.6	29.5	41.2	48.4
30–39 y	6.6	15.7	27.9	39.1	46.0
40–49 y	6.1	14.6	26.1	36.6	43.4
50–59 y	5.5	13.3	23.8	33.5	39.7
60–69 y	4.8	11.7	21.0	29.7	35.4
70–79 y	4.1	9.79	17.9	25.6	30.8
Younger age at diagnosis 30–39 y					
Older age at diagnosis					
30–39 y	6.2	14.8	26.5	37.1	43.7
40–49 y	5.6	13.4	23.9	33.7	39.9
50–59 y	4.8	11.6	20.9	29.6	35.3
60–69 y	4.0	9.6	17.5	25.1	30.2
70–79 y	3.2	7.7	14.3	20.7	25.2
Younger age at diagnosis 40–49 y					
Older age at diagnosis					
40–49 y	4.8	11.7	21.0	29.8	35.4
50–59 y	3.9	9.6	17.4	24.9	30.0
60–69 y	3.0	7.5	13.9	20.2	24.6
70–79 y	2.3	5.8	10.8	16.1	20.0
Younger age at diagnosis 50–59 y					
Older age at diagnosis					
50–59 y	3.0	7.5	13.8	20.0	24.5
60–69 y	2.2	5.6	10.5	15.7	19.5
70–79 y	1.6	4.2	8.1	12.4	15.8
Younger age at diagnosis 60–69 y					
Older age at diagnosis					
60–69 y	1.6	4.1	8.0	12.2	15.6
70–79 y	1.2	3.0	6.1	9.8	12.8
Younger age at diagnosis 70–79 y					
Older age at diagnosis					
70–79 y	0.8	2.3	4.9	8.1	10.9

Source: Reprinted with permission from Claus et al.[36]

in the *BRCA1* or *BRCA2* gene. (In these families, Bayesian analysis should be performed to determine a patient's chance for having inherited the gene, and the risk for ovarian, colon, and other mutation-related cancers should be addressed.) In addition, neither of these models incorporates other factors that appear to be correlated with breast cancer risk, such as lactation history, use of oral contraceptives, abortion, and diet.

An informal discussion among genetic counselors has revealed that both the Claus and Gail models are often used to provide the patient a risk "range" that incorporates both assessments, with an assumed true risk lying somewhere between.

BRCA Mutation Risk Models

While the Gail and Claus models are used to provide estimated risk for breast cancer, other models are available to estimate the likelihood of detecting a cancer susceptibility mutation for a patient who has a significant personal or family history of breast and ovarian cancer. Couch et al. produced tables to help estimate the probability that a patient carries a mutation in the *BRCA1* gene based on the number of breast and ovarian cancers in the family, as well as ethnicity (separate tables are available for women of Ashkenazi Jewish descent).[38] These tables were produced from data collected after genetic analysis of *BRCA1* in 263 women with breast cancer. Shattuck-Eidens et al. also provide a table for predicting prior probability of a mutation being present in the *BRCA1* gene.[39] The risks are based on the age and number of breast and ovarian cancers within a family. The Couch and Shattuck-Eidens models do not account for mutations in the *BRCA2* gene. To compensate for this limitation, some genetic counselors adjust the patient's risk by doubling the risk quoted in the tables.

Myriad Genetic Laboratories, which provides sequencing of the *BRCA1* and *BRCA2* genes in its patented BRACAnalysis, has produced its own model for estimating the likelihood of detecting a mutation in either a healthy or an affected patient.[40] The Myriad model, sometimes referred to as the Frank model, is based on information collected by the lab with samples submitted for testing and incorporates personal and family history of breast or ovarian cancer before age 50, as well as Ashkenazi Jewish ancestry. The tables are periodically updated on the company website at http://www.myriad.com.[41] History of male breast cancer is included in the most recent risk table.

The American Society of Clinical Oncology has recommended that *BRCA* genetic testing be considered for individuals whose family history of breast/ovarian cancer suggests a significant prior probability of a *BRCA* mutation, which many cancer genetics clinics translate as a risk of at least 10%.[42]

Additional Breast Cancer Risk Models

Computer programs also are available to help the clinician estimate a patient's risk for breast cancer or for carrying a *BRCA* mutation. These models are BRCAPRO and CancerGene.[43,44] The latter model generates multiple risk numbers using many of the models described earlier, including BRCAPRO. CancerGene can be obtained free

through http://www3.utsouthwestern.edu/cancergene/. These computer models and the risk assessment models discussed in the preceding paragraphs are designed for patients at risk for inherited breast cancer.

Hereditary Nonpolyposis Colorectal Cancer Models

For families with colorectal cancer careful analysis of the pedigree and review of pertinent medical records is the best guide for risk assessment and counseling. The Bethesda Guidelines and Amsterdam Criteria were established to assist in the diagnosis of families with or suspicious for hereditary nonpolyposis colorectal cancer (HNPCC). Originally written in 1991, the Amsterdam Criteria were modified in 1999 by the International Collaborative Group on HNPCC to account for the extracolonic cancers seen in some HNPCC families.[45,46] The original Amsterdam Criteria requires three relatives, one of whom is a first-degree relative of the other two, to be diagnosed with colorectal cancer in two generations. At least one of the cancers must have been diagnosed before the age of 40, and the diagnosis of familial adenomatous polyposis (FAP) must be excluded.[45] If a family meets these criteria, a diagnosis of HNPCC is assigned. The Modified Amsterdam Criteria consider the presence of any HNPCC-related cancer and extend the age of diagnosis to before age 50. Hereditary nonpolyposis colorectal cancer cancers include cancer of the colon, rectum, endometrium, ovary, stomach, small bowel, hepatobiliary tract, pancreas, ureter, and renal pelvis.[47,48]

The Bethesda Guidelines are less stringent that the Amsterdam Criteria and are used to determine which families warrant further evaluation.[49] Families who meet the criteria of the Bethesda Guidelines but do not meet Amsterdam Criteria should be considered for microsatellite instability (MSI) testing prior to genetic testing. Approximately 90% of HNPCC colorectal tumors exhibit MSI instability compared with only 15% of sporadic tumors. Hereditary nonpolyposis colorectal cancer is due to mutations that occur in one of several mismatch repair (MMR) genes. Clinical testing is limited to *hMLH1* and *hMSH2*, where approximately 60% of the HNPCC predisposing mutations occur.[50] Patients whose family history is strongly suggestive of HNPCC but who do not carry mutations in either *hMLH1* and *hMSH2* may qualify for research testing for one of the more rare HNPCC genes.

Patient Education

While the first half of the genetic counseling process relies on information collected from the patient, the remainder focuses on relaying the information back to the patient in a format that can be easily assimilated. During the information-giving portion of genetic counseling, cancer syndromes and genetics are described, risks are provided, screening and management issues are discussed, psychosocial issues are explored, and genetic testing may be offered. The information that had been collected allows the counselor to tailor the specific content to

reflect the patient's personal circumstances and meet his or her needs and expectations.

For example, a patient who has a family history that is significant for colon and endometrial cancer alerts the counselor to gather information from a local colon cancer support group and prepare visual aids for inherited colorectal cancer syndromes for use during the genetic counseling session. The counselor also collects information about the genetic tests available for colorectal cancer—such as the detection rate, cost, and turnaround time—to discuss with the patient. During the appointment, the counselor discusses the characteristics of cancer and the inherited colorectal cancer syndrome, the genetics and inheritance of known colorectal cancer susceptibility genes, genetic testing for familial mutations, and screening and management issues for colon and related cancers.

Each counseling session should include an overview of basic and cancer genetics in addition to education about risk, screening and management, and how genetic testing may influence each. A sample diagram that may be used to help explain how cancer susceptibility genes are passed on from generation to generation is provided in Figure 2.4.

Educating the patient about these topics and talking the patient through possible scenarios will provide him or her with the informa-

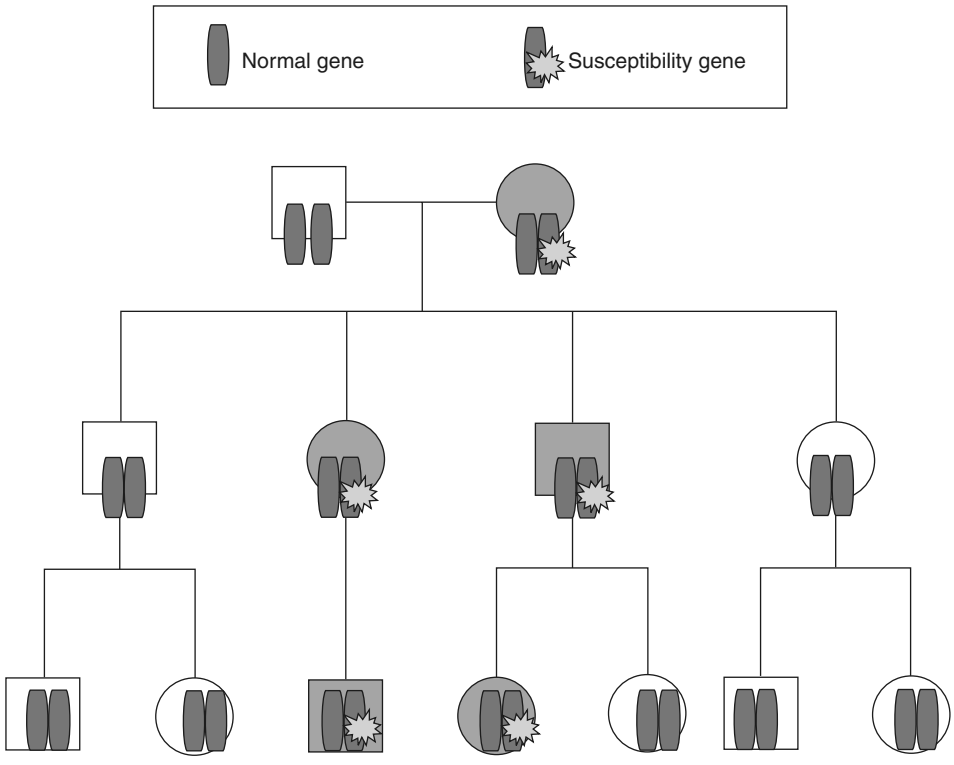


Figure 2.4 An inherited susceptibility mutation is passed down through the generations. Each child of an individual who carries the mutation has a 1 in 2 (50%) chance of inheriting the genetic mutation. Individuals carrying the mutation are at a significantly increased risk for cancer.

tion necessary to make an informed decision about genetic testing. As more cancer susceptibility genes are identified, genetic testing to determine a patient's risk for cancer will become increasingly common. During this time, patient education about these tests will remain important and should not be compromised.[51]

The benefits, risks, and limitations of genetic testing should also be discussed with each patient. Benefits of genetic testing may include relief from uncertainty, decreased anxiety, and an explanation for the cancer that seems to "run" in a family. The patient may also be more motivated to comply with screening recommendations if he receives a positive test result. Patients who learn that they did not inherit a known familial mutation also may be reassured that their children are no longer at increased risk.

Genetic testing also carries risks that should be discussed with the patient. The patient may experience increased anxiety, low self-image, and negatively altered familial or social relationships. Some patients who test negative when many family members have been affected by cancer experience a phenomenon known as "survivor guilt" (discussed below).

Although patients may express concern over the risk for discrimination with regard to health or life insurance coverage and employment, the federal and many state governments have enacted legislation to prevent discrimination based on genetic information.

The limitations of genetic testing in general refer to the limitations in current technology. For example, mutations in the *BRCA1* and *BRCA2* genes only account for about 8 of 10 hereditary breast cancers, while clinical testing for HNPCC is limited to 2 of at least 4 genes that can cause the phenotype.

Genetic Testing and Informed Consent

Genetic Testing

Genetic testing is a powerful option for many patients, but it is not appropriate for everyone. In 1996, the American Society of Clinical Oncology stated that a patient who is at risk for hereditary cancer should be offered genetic testing only when the following criteria are met[42]:

- The person has a strong family history of cancer or early age of onset of disease.
- The test can be adequately interpreted.
- The results will influence medical management of the patient or family member.

Through cancer risk counseling and assessment, genetic counselors play a significant role in determining which patients are candidates for genetic testing.

Minors

In general, genetic testing for adult-onset conditions like inherited cancer is not offered to minors to preserve individual autonomy and promote beneficence. Individual autonomy may be violated if testing is

performed without informed consent, which minors are legally unable to provide. Beneficence may be compromised if the information learned from genetic testing negatively impacts the way a minor is perceived or treated.[52–54]

There are exceptions to excluding minors from the cancer genetic testing process. For example, a child at risk for familial adenomatous polyposis (FAP) may benefit from information learned through genetic testing. FAP is a colorectal cancer syndrome that can cause malignancy as early as age seven. Children of an affected parent usually begin annual screening for polyps at a young age. A negative test result for a known familial mutation in the *APC* gene will relieve the child from invasive cancer screenings.

Determining Familial Mutations

Healthcare providers working with cancer families must understand that the most appropriate candidate for genetic testing is not always the patient. If the patient has a previous or current diagnosis of cancer, he or she may be an appropriate candidate for genetic testing. However, many individuals who present for genetic counseling have no personal history of cancer, while the family history is strongly suggestive of an inherited cancer syndrome. If the patient has never had a diagnosis of cancer, then the most appropriate person to be tested first is an affected relative.

Because a negative test result in a healthy patient is most informative when the familial mutation has been identified, the presence of an identifiable familial mutation should be determined before genetic testing is offered to unaffected family members. Testing an affected family member first will determine whether or not the family carries a cancer susceptibility mutation that is detectable by current technologies.

If the familial mutation has not been identified prior to testing a healthy patient, a negative test result may falsely reassure the patient of his or her cancer risk. While the negative test result has ruled out a mutation in the gene(s) tested, it has not ruled out the possibility of an inherited mutation in another gene or a genetic alteration not detectable by the lab methods employed during testing. Screening recommendations for the patient should therefore reflect the family history; the patient should not be assumed to have only the general population risk.

If the mutation has been identified in the family, a negative test result can be interpreted as a true negative. In this case, the patient no longer needs to undergo heightened surveillance. His or her risk for cancer has returned to that of the general population. However, the counselor must ensure that the patient understands that his or her risk of cancer has not been eliminated and that the patient should comply with cancer screening guidelines for the general population.

Informed Consent

Some patients may state early on that they "just want to be tested for the cancer gene." Although genetic testing can usually be performed on just a few tablespoons of blood, predictive genetic testing should never be conducted in the absence of pretest genetic counseling to ob-

Table 2.7 Elements of informed consent for germline DNA testing.

Information of the specific test being performed
Implications of positive and negative results
Possibility that the test will not be informative
Options for risk estimation without genetic testing
Risk of passing a mutation to children
Technical accuracy of the test
Fees involved in testing and counseling
Risks of psychological distress
Risks of insurance or employer discrimination
Confidentiality issues
Options and limitations of medical surveillance and screening following testing

Source: Reprinted with permission from American Society of Clinical Oncology.[42]

tain informed consent. In fact, most clinical and research laboratories require confirmation by the ordering physician that informed consent for genetic testing was obtained prior to performing the test (although documentation of informed consent is not always required by the lab).

Informed consent, an ethically mandated component of genetic testing, is obtained through the genetic counseling process by educating the patient about the benefits, risks, and limitations of genetic testing.[55] Many genetic counseling centers obtain written informed consent for each patient who pursues genetic testing.

In 1996, the American Society of Clinical Oncology presented the basic elements of informed consent for molecular testing for cancer susceptibility (Table 2.7).[42]

Results Disclosure and Interpretation

Genetic test results should be disclosed in person whenever possible. Questions often arise after the result has been disclosed, and it is best for the counselor to answer them in person, with access to visual aids if necessary.

The interpretation of how a genetic test result influences the patient's risk for cancer is often less than straightforward. A test result may be positive (a cancer susceptibility mutation is detected), negative (no mutation is detected), or of uncertain significance (an alteration is detected that is of unknown clinical significance). A negative test result may not mean that the patient did not inherit a cancer susceptibility mutation if the familial mutation had not been previously identified. A genetic variation of uncertain significance may open the door to research testing on other family members to clarify the meaning of the variation.

A face-to-face meeting with the patient allows the counselor adequate time, with the full attention of the patient, to review these issues. Now that the situation is no longer hypothetical, as it was during the pretest counseling session when each possible result with its implications and ramifications are outlined, the patient's perception may be altered, and different concerns may arise. Meeting with the patient in person provides the counselor with an opportunity to answer questions and detect and address any discrepancies in the patient's attitude.

Risk Management Discussion

The recommendations given to a patient for managing his or her risk are initially based on the family history. In general, a patient who has already been affected with cancer or who is at risk based on family history will be recommended to undergo heightened cancer surveillance. These recommendations may be modified based on information learned through genetic testing.

Most inherited cancers may be managed with either surgical or nonsurgical interventions. Surgical interventions include prophylactic mastectomy, oophorectomy, thyroidectomy, and colectomy, in addition to many others. Surgery may be recommended or chosen by a patient because of the high risk for a particular group of cells to become cancerous in combination with the poor detection rate associated with the surveillance methods available for that type of cancer.

Nonsurgical interventions include mammography, colonoscopy, ultrasound, and serum screens started at an earlier age and occurring at more frequent intervals than recommended for the general population. Chemopreventive drugs, such as tamoxifen, Roloxifene and Celebrex, are also options that may be discussed with the high-risk patient.

Psychological Counseling

One of the essential qualities of the clinician is interest in humanity, for the secret of the care of the patient is in caring for the patient."[56]—Francis W. Peabody, MD

Dealing with a personal or family history of cancer is likely to have had a significant impact on the patient's life experiences, lifestyle, and worldview. Assessing the patient's risk and incorporating knowledge about his or her genetic status may evoke further emotional responses. The genetic counselor should identify and prepare the patient for these responses and help him or her cope as they emerge.

There are multiple instances during the genetic counseling process that may lead to psychotherapeutic intervention. Strong emotions may emerge when a patient reflects on past experiences while gathering the medical history. Or, a patient may react strongly when he or she learns of information that is inconsistent with his or her own beliefs, such as how a cancer syndrome is inherited or what the true risk for developing cancer is after receiving a genetic test result. Regardless of what aspect of the genetic counseling process evokes these emotional responses, each response should be identified and addressed. When the psychotherapeutic aspect of the genetic counseling session is neglected or quickly skimmed over, the counselor has failed to complete his or her duties, and the patient receives a disservice.

Reflection

Beginning with the information-gathering process, patients may experience emotional reactions for which they were not prepared. Asking a woman about affected family members may cause her to recall her

own mother's death at a young age and a childhood that was filled with anguish, confusion, and despair. Her reflections may also remind her of her own young daughter, evoking further sadness and anxiety that her daughter will have to go through similar circumstances. In another example, a young man seeking information about his risk for colorectal cancer may realize his feelings of resentment toward his estranged father when he considers that he may have inherited from him the same gene that caused his sister's recent death. He tells the counselor that "cancer is probably the one thing my father left me."

Both of these scenarios demonstrate the powerful feelings that can surface when a patient is essentially required to reflect on emotionally painful events when collecting the family medical history. The counselor should spend adequate time to identify these emotions and allow the patient to explore and come to terms with each.

Reaction

During the risk assessment and patient education components of the genetic counseling process, patients may also experience strong emotional responses to information learned. A woman who comes from a small family in which her father, grandfather, and two uncles were affected with colon cancer may have falsely assumed she was less likely to develop cancer because she is of the opposite gender. In fact, she may be more concerned about her risk for breast cancer because of an aunt who was recently diagnosed at age 70. When her true risks are learned, she may express disbelief at the news and have difficulty reconciling the facts with her own experience. If she is unable to assimilate the information that she has just learned, she may be reluctant to comply with the more rigorous screening recommendations that she is given. The genetic counselor should allow adequate time during the counseling session to recognize and address these issues.

Although a strong emotional response can be expected when a patient learns that his or her risk is drastically different from what was perceived, some patient reactions are not so predictable. For example, a woman who spent many of the Saturdays during her childhood in attendance at funerals and memorials for aunts, cousins, her mother, and grandmother has always assumed that she too would succumb early in life to the cancer that claimed the lives of so many of the women in her family. She says, "All of us girls knew we would die before our own children grew up. That's just what happened in our family." When she learns that she is one of the few who did *not* inherit a familial mutation in the *BRCA1* gene, she has extreme difficulty adjusting to the reality that she may live for many more years and has, as she puts it, "escaped" the genetic legacy in her family. Suddenly, her life has been extended to include a period she never thought she would see. She has never considered how to spend her retirement years or imagined that she would live to see her grandchildren.

Whereas a medical professional delivering what is seemingly good news might assume a positive reaction from the patient—one that is

filled with relief and elation—this woman has learned information that has drastically altered her expectations and consequently has left her feeling extremely unsettled. Further exploration by the counselor reveals that she feels guilty for being offered the chance to experience a part of life that virtually none of the other women in her family were given. This patient needs help sorting through the powerful emotional response that this revelation has evoked, and it is the role of the genetic counselor to assist in this process either directly or by providing an appropriate referral.

Survivor Guilt

The response that the woman in the above scenario experienced is not uncommon. Known as survivor guilt, the reaction occurs when a patient learns that he or she has escaped a legacy of cancer or other chronic illness that has plagued most family members. The patient may not have expected such a reaction and may be uncertain how to handle it. Addressing discordant feelings and guiding the patient to understand the emotions are important roles of the counselor.

When the woman in the above scenario is allowed to talk through her reaction, with subtle probing and empathic responses carefully placed by the counselor, she admits that she considers herself the "strong one" in the family and a "caregiver" to her brothers and younger sisters. She explains that she has always tried to shelter them from difficult situations, beginning with their mother's own death, and she thinks she is emotionally stronger than her sisters and therefore would cope with cancer more easily than any of her siblings. She does not think it is fair that she is the one to evade this disease that is almost considered a right of passage for the women in her family.

The complexities of the emotions that may emerge during cancer genetic counseling are potentially profound. Neither the counselor nor the patient may be able to anticipate every response. The counselor, however, should be prepared to assist the patient in both the exploration and acceptance of each response so that the patient is able to make informed decisions about screening and management that are compatible with his or her own personal goals and value system. If the counselor feels unable to provide adequate psychosocial counseling, a referral to a psychologist or psychiatrist may be necessary.

Empathy

Achieving and expressing empathy is concordant with the psychotherapeutic model of genetic counseling. Empathic expression is an integral part of helping the patient cope with any emotions that may arise as a result of genetic counseling. Described by Bellet and Maloney in 1991 as "the capacity to understand what another person is experiencing from within the other person's frame of reference," empathy is achieved when the counselor expresses an understanding of what the patient is feeling.[57]

To express understanding, the counselor must recognize and pay attention to both verbal and nonverbal cues from the patient. Verbal cues include words like "frustrated," "surprised," "angry," "worried," and "anxious" and nonwords such as a loud sigh or grunt. Nonverbal cues are exhibited through silence or by body language—she may express defeat by slumping her shoulders and casting her eyes down, or he may indicate anger by crossing his arms and sitting far back in his chair. Watching and listening for these cues will provide the counselor with information that is necessary to produce an appropriate empathic response. The counselor should then consider the significance of what has been perceived and accordingly frame a response that acknowledges these perceptions.

The empathic response should not be confused or substituted with sympathy, where the focus of the counselor may turn (even if only for a moment) to himself. Achieving empathy does not imply that the counselor be sympathetic or have a personal understanding of what the patient is experiencing.[15] Therefore, it is possible for any person to produce an empathic response toward another human being. In genetic counseling empathy simply requires that the counselor recognize an emotional reaction and discern its significance to the patient's overall affect. Acknowledging to the patient what has been observed and discerned then produces the empathic response.[15]

Relationships

Learning about personal risks for inherited cancers may not only alter a patient's self-image and perception but also have an impact on the patient's interpersonal relationships. The knowledge that one has inherited a genetic mutation from a parent also implies that one's children are at risk, and the difficulties experienced when coping with anger toward the parent may be amplified by guilt that a child is also at risk. Questions and concerns that may arise include:

- How do you tell your spouse or child that your risk for cancer—and perhaps theirs—is much higher than you thought?
- What obligations do you have to tell your fiancé or spouse that your future children may inherit your cancer susceptibility gene?
- How do you explain everything to your best friend so that he or she understands what you are going through?
- How do you approach your distant cousin, who is battling the same type of cancer that killed your father, about genetic counseling for testing that may provide answers for you and your siblings?

Referrals

Any genetic counselor should be able to recognize his or her limitations when dealing with the complexity of emotions that may arise during the genetic counseling process. In some instances, a referral to an outside psychologist or psychiatrist may be best. Part of the genetic counselor's role is to recognize his or her limitations and provide a referral when additional psychological support or therapy is deemed necessary.

Genetic Counseling Case Presentations

Hereditary Breast/Ovarian Cancer

In the scenario presented in Figure 2.5, the patient is a 24-year-old female who learns through genetic counseling that her family carries a *BRCA1* mutation; however, she did not inherit it. Although her father carries no cancer diagnosis, two of his three sisters were diagnosed with premenopausal breast cancer, and his mother was affected with breast and ovarian cancer before age 45.

According to the Myriad model, the patient has a 16.4% risk for carrying a deleterious mutation in either *BRCA1* or *BRCA2*. Her risk of breast cancer as predicted by the Claus model is 0.6% by age 59, 2.0% by age 39, 5.2% by age 49, 9.8% by age 59, 14.7% by age 69, and 18.4% by age 79. The limitations of the models are discussed, and the patient is counseled about her mendelian risk if a *BRCA1* or *BRCA2* has caused the cancers in her family: Her father has a 50% risk of having inherited the mutation from his mother, while the patient's risk is 25% ($0.5 \times 0.5 = 0.25$). She is further counseled that, if she has the mutation, her risk for breast cancer is approximately 85%, while her risk of ovarian cancer is 16% to 60%. Her risks for colon and pancreatic cancer may also be increased.*

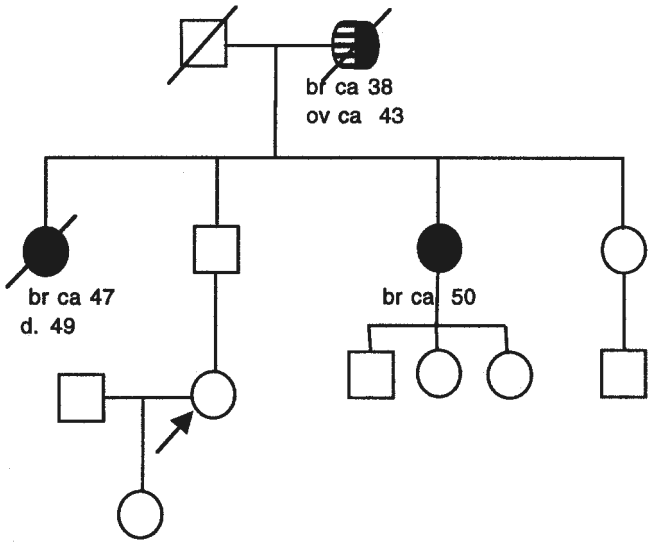


Figure 2.5 A healthy patient presenting with a family history of breast and ovarian cancer that is caused by a germline BRCA1 mutation.

*If the patient were of Ashkenazi Jewish descent, her risks would be modified. Approximately 1 in 40 individuals of Ashkenazi Jewish descent carries a cancer susceptibility mutation in either *BRCA1* or *BRCA2*, with three founder mutations accounting for the vast majority. The risk for breast cancer is less than that of a non-Ashkenazi Jewish mutation carrier. The risk for breast cancer is 45%, while the risk for ovarian cancer is 15%. This information is important to communicate to appropriate patients because it may influence management decisions.

The benefits, limitations, and risks of genetic testing are reviewed, and the benefit of first testing her living affected aunt is discussed. Screening recommendations based on her family history alone are reviewed. She is also guided through different scenarios regarding her possible mutation status and how screening and management recommendations may be influenced based on her genetic status. She expresses her interest in testing, as well as her concerns over the risks to her young daughter when she is older.

The initial counseling session ends when the patient decides to contact her aunt regarding her willingness to pursue genetic counseling and testing. The aunt is subsequently tested and learns she carries a deleterious mutation in *BRCA1*. The patient returns for testing, and at her results disclosure session 3 weeks later she learns that she does *not* carry the mutation. Her risks for cancer return to that of the general population, and appropriate screening recommendations are made.

(Note that if the aunt had not agreed to testing, the negative test result in the patient would have been less informative. Although no mutation was found in *BRCA1* and *BRCA2*, the possibility of another gene being responsible for the cancers in her family would not have been ruled out, and her screening recommendations would have reflected her family history. She would have been assigned to the high-risk category and recommended to begin mammograms at age 28 [10 years prior to her grandmother's breast cancer diagnosis, the youngest diagnosis in the family] and heightened surveillance for ovarian cancer with annual pelvic exams, transvaginal ultrasounds, and serum CA125 measurements.)

Although the patient has learned that she has not inherited the cancer susceptibility mutation that has caused the cancer in her family, her paternal cousins are at risk for the identified genetic mutation. After learning about her risk, a female cousin undergoes testing and learns she is positive for the mutation. She is anxious over her heightened risks and meets with a surgeon to discuss prophylactic mastectomy and oophorectomy. She decides that she will follow the recommended high-risk screening procedures until she has completed childrearing, at which time she will return to discuss prophylactic oophorectomy. She has been told that this option will reduce her risk of ovarian cancer by 90% and her risk for breast cancer by as much as 70%.

Hereditary Nonpolyposis Colorectal Cancer

In the scenario presented in Figure 2.6, the patient is a 30-year-old male seeking information about his risk for colon cancer. A paternal aunt and uncle, his grandmother, and a great aunt all presented with cancers consistent with HNPCC. His father had a small number (<20) of precancerous polyps detected on exam at age 53 and elected to have a colectomy. The paternal cousin with "kidney problems" may represent an extracolonic manifestation of HNPCC. The most frequent extracolonic tumors seen in the syndrome include uterine (35%) and ovarian (10%). Other HNPCC-associated cancers involve the stomach, brain, small intestine, liver, and urinary tract, each occurring in less than 5% of patients.

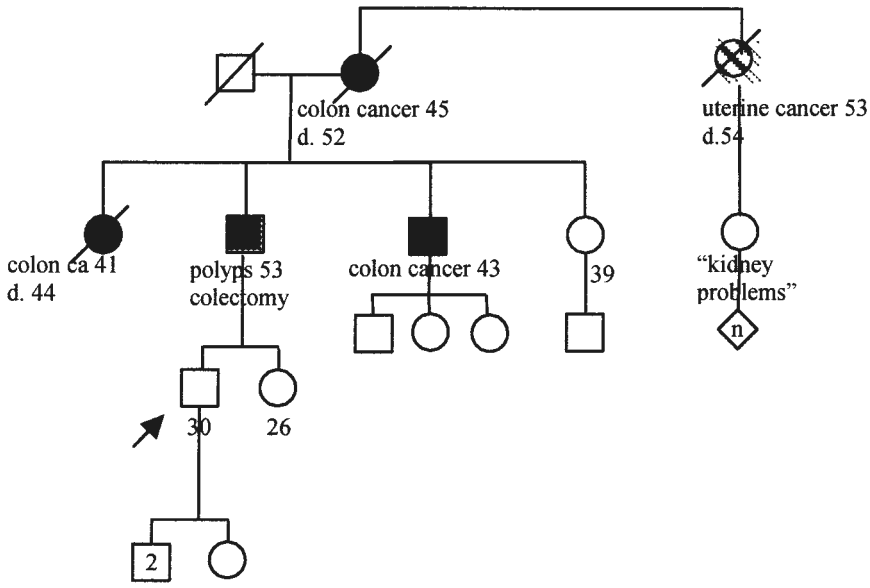


Figure 2.6 Patient whose family history indicates a diagnosis of HNPCC.

The patient is counseled about the strong suspicion of HNPCC in his family, and his risks are discussed. He is counseled about his 50% risk for having inherited a HNPCC mutation from his father, and his cancer risks are reviewed. He reveals that his sister is estranged from the family, and he has not spoken to her in a number of years. He does not know if he can or is willing to contact her about her own risks. Genetic testing for the *MSH2* and *MLH1* genes is discussed (*MSH2* and *MLH1* cause the majority of HNPCC cases and are the two genes for which clinical testing is available).

The patient is interested in genetic testing, and the utility of testing his father first is reviewed. The initial counseling session comes to an end, and the patient contacts his father during the following week to assess his willingness to pursue genetic testing. His father declines. The patient returns a few weeks later and decides to proceed with testing, understanding the limited informativeness that a negative test result would provide. He returns 3 weeks later and learns that no mutation was detected.

Screening recommendations are made based on his family history because the possibility of a germline mutation in one of the other HNPCC genes could not be ruled out. The patient will begin annual colonoscopy at age 31.* If polyps are detected, he will consider surgery to remove his colon before malignancy occurs. His sister's risks for uterine and colorectal cancer are also discussed, and he decides that

*Some cancer genetics centers also recommend screening for the less frequent extracolonic cancers, although the clinical usefulness of these screening exams in high-risk patients is unclear. Screening for the less frequent HNPCC extracolonic cancers may include annual upper endoscopy, small bowel x-ray, urine cytology, liver function panel, and neurological function examination.[58]

he will try to locate her to inform her of the risks. He is given written materials that outline both his and his sister's screening recommendations. The sister's recommendations also include screening for uterine and ovarian cancer by pelvic exam, transvaginal ultrasound, and endometrial aspiration every 1 to 2 years starting at age 25 to 35.

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3

Ethical Issues in Genetic Testing for Cancer Susceptibility

Terrence F. Ackerman

The confluence of numerous factors presages the growing role in clinical medicine of genetic testing for inherited cancer susceptibility. Research in molecular genetics is facilitating the localization and sequencing of new cancer susceptibility genes. Critical issues regarding the importance of specific mutations within genes, the penetrance and expressivity of these mutations, the value of medical interventions in reducing cancer risks, and appropriate methods of counseling patients are being addressed in carefully designed studies. At the same time, more efficient technologies for DNA analysis are being developed that will enable these tests to be performed at a more reasonable cost, while yielding a higher percentage of informative results. Recognizing the considerable profit potential of widespread use of tests for inherited cancer susceptibility, aggressive marketing by commercial genetics laboratories is increasing pressure on physicians to apprise their patients of the availability of testing. As more effective interventions are identified for reducing risk and treating disease, managed care organizations, health insurers, and self-insured employers may also encourage testing as a means to control healthcare costs.

The capability to perform these tests possesses considerable promise for enhancing the clinical care of patients. If effective preventive measures, surveillance regimens, and/or prophylactic interventions can be devised to reduce the risk of the onset of cancer or facilitate early identification and treatment, genetic testing will enable patients to assume a substantial measure of active control over their inherited cancer risk. At the same time, these developments present perils that may undermine the intended benefits of their clinical application. Uncertainties abound regarding the medical, psychological, familial, and social implications of identifying persons with inherited cancer susceptibility. These uncertainties generate complex questions regarding the contours of our moral obligations in the context of genetic testing. Critical questions arise regarding the moral obligations of healthcare providers, patients, and society.

These moral questions can be grouped around the requirements of three basic moral principles. The first is the principle of beneficence.

In the context of the therapeutic relationship, this principle requires that healthcare providers protect and promote the welfare of patients. Questions arise about the conditions under which healthcare providers should recommend or offer genetic testing for inherited cancer susceptibilities to protect or promote the welfare of patients. These questions are complicated by inadequacies in available testing methodologies, uncertainties about the significance of specific mutations, the limited efficacy of interventions designed to control risk of cancer, and challenges in devising effective counseling strategies. The second principle is that of respect for the autonomy of patients. This principle requires that interactions in the therapeutic relationship be consistent with the values and goals of the patient. The moral importance of respecting the values and goals of individual patients generates important issues regarding the requirements for informed consent and genetic counseling, the limits of confidentiality, and the rights of patients to request testing for their children and fetuses. The third principle is that of justice or fair treatment. This principle requires that important goods be distributed in ways that treat persons fairly vis à vis one another. In the context of genetic testing for inherited cancer susceptibility, concern exists that testing results may be used to deny persons access to important goods such as health insurance and employment. Thus, critical issues arise regarding the criteria that should be used to determine the fair distribution of these goods to persons with inherited cancer susceptibilities.

In the subsequent analysis, the implications of these principles for the practice of inherited cancer susceptibility testing are explored. Because of the uncertainties regarding the benefits of testing, the rapidly developing knowledge in this field, and the variety of contexts in which testing might be undertaken, concrete directives for the resolution of the issues cannot be provided. Rather, the objective is to provide a conceptual framework for analyzing specific moral issues as they arise in clinical practice.

Patient Welfare and the Recommendation for Testing

In the context of the therapeutic relationship, the moral principle of beneficence enjoins the healthcare provider to protect and promote the welfare of patients. Offering a specific intervention to patients is appropriate when two basic conditions are satisfied: The risks are justified by the anticipated benefits, and the risk–benefit ratio of the intervention is at least as favorable as any alternative course of action available to the patient. Genetic testing for inherited cancer susceptibility should be recommended or offered only if it satisfies these basic criteria.

The potential benefits of genetic testing relate to either reassurance about the absence of elevated cancer risk that may derive from negative test results or the increased control of cancer risk that might be possible based on positive test results. When test results are negative, absence of elevated cancer risk is confirmed only if the specific muta-

tion that is inherited has already been clearly identified in another family member and is absent in the patient tested. In the absence of this information, negative test results must be considered merely uninformative. There are numerous reasons why test results may be uninformative.[1] The patient may have a specific mutation in a recognized cancer susceptibility gene that is not detected by the testing method employed, there may be a mutation in a rare or as yet undiscovered gene, or there may be a variant identified in an established susceptibility gene whose clinical significance is not at present known. When negative test results are merely uninformative, the anticipated benefit of relieving concern about elevated cancer risk is not realized. Moreover, if the family history of cancer suggests a clearly elevated cancer risk despite the occurrence of uninformative test results, the recommendations for monitoring may be similar to those for patients who have positive test results. The upshot is that the potential benefits of a negative test result may be severely attenuated if the results must be interpreted as merely uninformative and there is a family history strongly suggestive of inherited cancer.

In the case of clearly positive test results, the potential benefits of the information depend on the ways in which patients can utilize the information either to reduce their risk of cancer or facilitate early diagnosis and treatment. In general, there are three categories of interventions that might be used to accomplish these goals: lifestyle changes related to matters such as diet and exercise, increased monitoring and surveillance for the onset of cancer, and the use of prophylactic regimens. However, no potential risk reduction associated with lifestyle changes for persons with inherited cancer susceptibility has been clearly established.[2]

The potential benefits of monitoring or surveillance relate to identification of cancer in its early stages and timely treatment resulting in decreased morbidity and mortality. In evaluating these potential benefits, several points are relevant. First, for some tumors related to inherited cancer susceptibility, aggressive surveillance is clearly associated with decreased morbidity and mortality. This benefit seems most apparent in familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).[3] Aggressive surveillance facilitates the identification of colorectal lesions of various types requiring surgical intervention. Monitoring is essential to preventing early death associated with these lesions. Second, for other cancers it may be more difficult to monitor for early tumor development, as in the case of ovarian cancer associated with the *BRCA1* mutation.[4] Third, there are cases in which the potential benefits of standard monitoring techniques remain to be more clearly defined. For example, it is not yet clear what advantage might accrue for early detection of breast tumors by mammography in women with *BRCA1/BRCA2* who are less than 40. Fourth, it is often not clear what advantages are obtained for genetically predisposed persons from early identification with respect to the treatability of cancer and reduction in morbidity and mortality.

Prophylactic interventions may represent the most important means for reducing the risk of disease available to persons who test positive

for inherited cancer susceptibility. For example, in the case of breast cancer susceptibility chemoprevention and prophylactic surgery may provide substantial reduction in the risk of disease. A major clinical trial of tamoxifen established that its use reduced the risk of breast cancer by 49% over a 5-year period in women with an elevated risk of cancer by family history.[5] Similarly, studies of bilateral prophylactic mastectomy suggest a substantial reduction in risk for breast cancer.[6] Bilateral prophylactic oophorectomy may possess even higher rates of risk reduction for ovarian cancer associated with *BRCA1*.[7] Nevertheless, prophylactic interventions possess important limitations as well. While tamoxifen may offer substantial reduction in the risk of breast cancer, its use creates additional health risks. In the Breast Cancer Prevention Trial, women over 50 who took tamoxifen quadrupled their risk of uterine cancer and tripled their risks of thromboembolisms in the lungs or major veins.[5] The risk of breast cancer in women who opt for bilateral prophylactic mastectomy may remain as high as 10% to 15%, depending in part on the surgical approach utilized.[6,8] Similarly, it appears that there is a small residual risk of ovarian cancer for women with *BRCA1/BRCA2* who undergo bilateral prophylactic oophorectomy.[4] At the same time, early surgical menopause may confer an increased risk of cardiovascular disease and osteoporosis. Thus, current prophylactic treatments do not eliminate the risk of developing cancer, while they may also confer additional risks of serious health problems.

The potential benefits of reducing cancer-associated health risks must also be balanced against nonmedical risks associated with receiving positive test results. These risks can be categorized as psychological, familial, and social. Psychological risks include reactions such as anger, depression, persistent worries, anxiety, guilt, and sleep disturbances.[9] Although early studies in adults who received positive test results for genetic susceptibility to Huntington's disease suggested that satisfactory psychological adjustment was eventually achieved, the generalizability of these results is uncertain because of the pronounced self-selection apparent in the small number of at-risk individuals who decide to undergo testing.[10,11] By contrast, initial studies in persons testing positive for the p53 mutation and breast cancer susceptibility suggest more substantial rates of psychological distress.[12]

A second group of risks is associated with the potential negative impact of testing on familial relationships. Unlike much health information that pertains only to the individual patient, genetic information carries implications for the health status and welfare of other family members as well. When a patient contemplates testing for inherited cancer susceptibility, other family members may be deeply distressed about the prospect of finding out whether the family might be affected. When a patient has a positive test result, family members may be angry and resentful that the patient has forced them to confront the possibility of their own genetic risk status. Family members who test positive may experience resentment toward those who do not, while those who test negative may feel "survivor guilt" for having escaped the increased cancer risk that must be confronted by other family members.

The emotional divide between family members who test positive and those who do not may create difficulties in communication. Moreover, these various reactions may exacerbate previously existing tension or conflicts within families. Finally, differential treatment of family members by one another may occur with regard to matters such as inheritance and educational opportunities based on the fact that some may have a more favorable life expectancy than others.

A third category of risks relates to the social implications of testing positive for inherited susceptibility to cancer. Persons may be denied access to insurance, employment, and educational opportunities based on positive test results.[13] In addition, members of particular ethnic groups who have a high incidence of an inherited cancer susceptibility may suffer more subtle forms of discrimination or social stigmatization based on public perceptions of their "defects." These difficulties may impair the opportunity of persons to achieve financial, educational, career, and other social goals.

This enumeration of the potential risks and benefits associated with genetic testing for inherited cancer susceptibility carries important implications regarding the conditions under which testing should be recommended or offered to promote the welfare of patients. First, there are cases in which testing results may provide clear guidance for subsequent medical monitoring that may decrease morbidity and mortality for some tumors associated with inherited cancer syndromes. The clearest example is surveillance for colorectal lesions of various sorts associated with FAP and HNPCC. Recommended surveillance provides a critical guide to the timing of colon surgery to prevent death from colorectal cancer. Second, for most cases the favorability of the risk–benefit ratio associated with testing is often not so transparent that any reasonable person would judge that testing promotes his or her interests. As we have seen, the potential benefits of testing for the control of cancer risk are typically limited. Monitoring for particular tumors may be difficult, or the benefits of monitoring for improving the treatability of cancer may not be established. Prophylactic interventions may have limited benefits while possessing substantial risks. At the same time, there are significant nonmedical risks associated with receiving the results of testing, particularly if they are positive. Existing uncertainties about the probability of achieving the benefits while avoiding the associated risks exacerbate the problem of making definitive risk–benefit assessments about the advisability of testing. Third, the reasonableness of testing for individual patients will integrally depend on the value or weight that they assign to the particular benefits and risks associated with testing. For example, a person who places a high priority on avoiding conflicted relationships may choose not to undergo testing for *BRCA1* when faced with family opposition, even if he or she acknowledges that some potential health benefits might be obtained. Similarly, a woman with a family history of breast cancer may find the potential benefits of testing negligible if she would likely decline prophylactic mastectomy or oophorectomy for cosmetic or reproductive reasons or considers chemoprophylaxis to involve unacceptable, additional health risks.[14] Thus, the specific values and goals

of the patient may bear heavily on the determination of whether the risks associated with genetic testing for inherited cancer susceptibility are outweighed by the anticipated benefits for the control of cancer risk. Fourth, aside from the weighting of the particular benefits and risks of genetic testing, persons may have different general values about seeking and using medical information in planning their lives. Psychological research has suggested that some persons are information seekers who cope by reducing uncertainty about their health status, while others are information avoiders who cope by maintaining uncertainty.[15,16] For persons who are information seekers, even positive results of genetic testing may enhance their sense of well-being and personal control over their health. But for persons who are information avoiders, confronting genetic information about disease susceptibilities may pose numerous perceived threats.[17] One is the perceived threat to life and the maintenance of bodily integrity that may occur if an increased cancer risk is confirmed. A second is the perceived threat to self-concept and future plans. Learning that one has a genetic cancer susceptibility may cause reconsideration of self-image, occupational goals, and one's current conception of the extent of personal control over the course of life. Another, already discussed, involves perceived threats to emotional equilibrium. Potential candidates for genetic testing may have limited psychological resources for handling intense emotional reactions such as depression, anxiety, anger, and a sense of failure. Finally, positive test results may generate perceived threats to the fulfillment of social roles and activities. For example, persons may feel that previous career goals are unrealistic or they may experience ambivalence about the appropriateness of parenthood. For information avoiders, genetic testing may thus pose major coping challenges for which they possess limited psychological resources and that lead them to adversely assess the value of securing predictive information about their health. These considerations may partly explain the observation that, while many persons express an interest in genetic testing when the opportunity is posed in the abstract, far fewer actually undergo testing when it becomes available.[18]

The net import of these considerations is that the determination that the risks of genetic testing are outweighed by the anticipated benefits for particular patients, and that the risk–benefit ratio of testing is more favorable than the alternative of not testing, often cannot be made based on simple medical indications. Rather, these judgments must incorporate an understanding of how individual patients weigh the benefits and risks of testing in terms of their own values and goals. This understanding must unfold in the interactive process in which the implications of genetic testing are explored with the patient. These considerations underscore the crucial importance of the informed consent and genetic counseling process.

Role and Limits of Autonomy in Testing

The moral principle of respect for autonomy requires that we protect and promote the capacity of persons to deliberate and act on their own

values and goals. In the context of the therapeutic relationship, the moral importance of respecting the values and goals of the patient gives rise to several specific moral duties, including the requirements to secure informed consent for medical interventions and protect the confidentiality of private information revealed by the patient. The common feature of these rules is that they enable patients to exercise control over the conditions and circumstances under which they will permit others access to their bodies or personal information about themselves.

The informed consent and genetic counseling process facilitates the ability of persons to deliberate and act on their own values and goals only if several conditions are satisfied.[19] First, those items of information must be disclosed that a reasonable person would need to know in making a decision about whether to undergo the proposed medical intervention. Second, the process must result in adequate comprehension by the patient of the information disclosed. While the disclosure requirement is usually emphasized in the preparation of consent documents, the comprehension condition is no less important. Unless patients adequately comprehend the information disclosed, they cannot use it effectively to determine whether the proposed intervention comports with their own values and goals. Moreover, insofar as comprehension is a necessary condition of securing an adequately informed consent, the healthcare provider has the responsibility for assuring that the patient achieves a satisfactory understanding of the information disclosed. Third, the agreement or refusal of the patient to proceed with the proposed intervention must be made voluntarily, that is, the decision of the patient must reflect his or her own values and goals rather than being determined by the coercion, manipulation, or undue influence of other persons. Last, the process must conclude with an understanding and intentional authorization by the patient of the proposed intervention.

In clarifying the healthcare provider's obligation to respect the patient's autonomy, it is important to distinguish between the consent process that culminates in an understanding, voluntary authorization by the patient and the signing of the informed consent form. The latter action provides confirmation or documentation that the informed consent process has occurred and has issued in a positive decision by the patient to authorize the intervention. The signing of the form is not equivalent to informed consent in that the mere act of signing may or may not reflect an understanding and voluntary decision by the patient to authorize the proposed intervention. Rather, informed consent and genetic counseling constitutes a process of disclosure, comprehension, and voluntary choice culminating in an understanding and intentional authorization of the intervention. Unless the process satisfies the conditions described above, the signing of the consent form does not reflect satisfaction of the healthcare provider's duty to secure the informed consent of the patient.

Satisfaction of the disclosure condition for informed consent involves communication of numerous categories of information that a reasonable person in the patient's position would need to know in making a decision about testing for inherited cancer susceptibility.[20,21] One cat-

egory involves information about testing procedures, including the accuracy and limitations of the test itself, as well as the procedures for pre- and posttest counseling. The possible outcomes of testing in terms of true positives, true negatives, and merely uninformative results must be explained. The potential benefits of either positive or negative results should be explored, including the potential usefulness and limitations of interventions for prevention, medical surveillance, and prophylaxis. The potential risks of testing must also be examined, including psychological effects, familial conflicts, and the social risks of insurance and employment discrimination. Similarly, the possible implications of testing for the risk status of the patient's children should be addressed. Provisions for protecting the confidentiality of the information secured through testing must be addressed, including the conditions under which results would be disclosed to insurers, employers, or other third parties. The patient should also be aware that test results may be relevant to the health of other family members, and they should be invited to consider whether they would be willing to share this information with relatives. The alternatives to testing must be explored, especially the ability to estimate the risk of cancer and institute appropriate monitoring and surveillance in the absence of testing. Finally, the costs of testing and fees associated with counseling must be explained.

Although disclosure of pertinent information in the counseling process is a necessary condition of adequately informed consent, it is not sufficient. Assessment must also be made of the extent to which patients comprehend the information disclosed. This assessment requires that the process of genetic counseling be substantially interactive.[22] One component of this interactive assessment involves inviting patients to ask questions about information that they do not understand. However, it is well established that patients often do not ask questions even when they do not comprehend information disclosed. A more critical element of the assessment involves the active querying of patients to determine their level of comprehension. A useful approach to this process involves asking patients to put in their own words their understanding of the information presented. In some settings, formal testing may also be useful in identifying items of poorly comprehended information that may need to be revisited with patients.

Finally, assuring voluntary consent by patients involves assessment of whether the factors motivating the patient's decision to undertake genetic testing reflect their own values and goals. One component of this process involves an interactive probing of the reasons patients are seeking testing and the determination that these reasons do not represent a substantial or controlling influence of other persons. This does not mean that patients cannot agree to undergo testing primarily to meet the health needs of other family members, but rather that the commitment to meet those needs must be an important component of their own values and goals. A second critical factor in assuring an adequately voluntary consent is the commitment of the healthcare provider to demur from being directive in the counseling process. This view is contrary to some recent suggestions that the model of nondi-

rective counseling, born in the era when genetics counseling focused on reproductive decision making, may need to be modified with regard to decision making about genetic testing for disease susceptibility.[23,24] However, as we saw above, determination that the risks of genetic testing are outweighed by the anticipated benefits depends in substantial part on the weight that individuals attach to the potential benefits of testing for control of their cancer risks, as well as to the various risks of adverse psychological, familial, and social consequences that may ensue from testing. Moreover, persons who are information avoiders rather than information seekers place considerably different general weight on the merits of securing predictive information about their risks of disease. Thus, in the absence of definitive medical indications for testing, counseling that is directive may encourage persons to make decisions for cancer susceptibility testing that do not conform to their own values and goals.

Respect for the autonomy of patients also requires that healthcare providers protect the confidentiality of medical information acquired in the course of the therapeutic relationship. There are important reasons for the strong moral presumption in favor of maintaining confidentiality.[25] One is that respect for patients requires that the conditions and circumstances under which private information is revealed to other persons must accord with their own values and goals. If persons are not able to exercise such control, then their ability to pursue their life plans in the manner of their own choosing may be seriously impaired. Another reason for the strong presumption in favor of protecting confidentiality is that failure to do so may seriously compromise the ability of healthcare providers to secure the information from patients necessary to provide effective and safe medical interventions. If patients are unable to trust healthcare providers to protect sensitive personal information from third parties, then they may not be forthcoming with the information needed to make accurate diagnoses and appropriate recommendations for treatment. Indeed, patients may be reluctant to share certain sensitive medical problems with healthcare providers at all. Finally, respect for confidentiality reinforces the recognition that the primary obligation of healthcare providers is to protect and promote the interests of the patient, and satisfying the interests of other parties must be secondary to this essential focus.

Nevertheless, information derived from genetic tests for inherited cancer susceptibility is different from ordinary medical information in that it carries implications for the health status of family members as well. This information may be useful to family members in preventing serious risk of harm. A strong argument can be made that patients have a moral duty to disclose information about test results to their family members if the latter desire to receive such information. It can also be maintained that healthcare providers have a duty to emphasize the importance of this duty in their counseling of patients. While surveys reveal that most patients are willing to disclose relevant information to family members, it is clear that this is not always the case.[26] Thus, the question arises as to whether it is ever permissible for the healthcare provider to violate the moral presumption in favor of protecting the

confidentiality of the patient to provide pertinent information to family members.

It is widely accepted that the moral duty to protect the confidentiality of patients is not absolute. The underlying idea is that the scope of the moral right to exercise our autonomy does not extend to circumstances in which its exercise may cause serious and irreversible harm to others. When disclosure of confidential information may prevent serious and irreversible harm to other individuals, these interests may sometimes outweigh the duty to respect the patient's request to maintain confidentiality.[27] This exception has been recognized in case law.[28,29] In addition, healthcare providers are typically under statutory obligations to report specific information received in the therapeutic relationship related to contagious diseases, child abuse, gunshot wounds, and conditions that are not compatible with safe driving. However, because of the strong moral reasons favoring protection of patient confidentiality, the conditions under which confidentiality may be violated in individual cases not covered by legal reporting requirements must be precisely and narrowly construed. Specifically, it is morally permissible to violate confidentiality only if (1) nondisclosure will result in serious and irreversible harm to a third party, (2) the disclosure of the information has a strong probability of preventing that harm, (3) there is no available alternative for preventing the harm, (4) the disclosure of confidential information is limited to that necessary to prevent the harm, and (5) it is likely that the disclosure will result in a net balance of good over harm.[30]

The crucial question is whether these conditions are ever satisfied with regard to the nonvoluntary disclosure by the healthcare provider of confidential information related to the results of genetic testing for inherited cancer susceptibility. With respect to the latter, it seems clear that usually one or more of the conditions are not satisfied. Typically, the penetrance of the gene is incomplete. For example, in the case of *BRCA*1 the lifetime risk of breast cancer is probably in the range of 60% to 85% while the risk of ovarian cancer may not exceed 40%.[31–33] As a result, it cannot usually be claimed that nondisclosure of positive test results to an unsuspecting relative will, in fact, result in the serious and irreversible harm posed by the diagnosis of cancer. In addition, it is often not clear that disclosure to potentially affected relatives will prevent the harm of diagnosis of cancer from occurring. For example, as noted earlier in the case of *BRCA1*, careful monitoring to provide early detection may not result in more effectively treated disease, especially with respect to ovarian cancer. Likewise, chemoprophylaxis appears to reduce the risk of the disease by less than 50%. Even prophylactic surgery does not eliminate the risk of breast or ovarian cancer in residual tissue. Thus, nonvoluntary disclosure of confidential information regarding positive results of testing may not carry a sufficiently high probability of preventing the harm to family members to warrant violation of confidentiality. Finally, there are typically alternatives available for preventing the potential harm to family members. If they are aware of their own family cancer history, they may educate themselves about whether they

may be at increased risk of having an inherited susceptibility and might profit from undergoing genetic testing. There are frequent discussions of these matters in popular magazines, on the Internet, and on television for persons who are motivated to learn more about how to control their cancer risks.

Having made these general points, it is clear that cases may occur in which the conditions for violating confidentiality might be satisfied. Suppose, for example, that a woman is planning to undergo a bilateral prophylactic mastectomy, based on a strong family history of breast cancer, even though her results for *BRCA1* and *BRCA2* testing were uninformative. In the meantime, her estranged sister who was diagnosed with early-onset breast cancer is tested at the same clinic and a specific mutation is identified. This introduces the possibility of retesting the first sister to determine whether she carries the specific mutation now identified in the family lineage. The estranged sister balks at communicating the result to her sibling. In this case, there may be strong grounds for overriding the presumption in favor of maintaining confidentiality. The first sister is contemplating major surgery whose harms might be averted if she is retested and found to be negative for the family mutation. There is no alternative to preventing this harm short of compromising her sibling's confidentiality. In this case, the grounds for overriding confidentiality may exist. However, it remains true that the conditions for overriding confidentiality will normally not exist in the context of genetic testing for inherited cancer susceptibility and that the strong general presumption in favor of protecting confidentiality should be maintained.

Another important autonomy-related issue concerns the right of parents to request genetic testing of their children for inherited cancer susceptibility. Parents who are determined to have genetic susceptibility to cancer usually express deep concerns about the status of their children, and some request that their children be tested.[34,35] Moreover, existing survey data suggest that a substantial percentage of physicians and other healthcare providers are willing to accede to such requests.[36] Despite this fact, numerous professional guidelines have suggested that clear limitations should be placed on the conditions under which such testing is performed.[36–38]

Parents are in general assigned wide discretion in making healthcare decisions for their children. However, the scope of parental autonomy is properly restricted in circumstances where its exercise might cause serious and irreversible harm to their children. For example, parents are permitted by law to reject recommended medical treatment for their child unless the child is likely to die without the recommended intervention, the intervention itself will not seriously endanger the life of the child, the proposed intervention is likely to return the child to a normal state of health, and there is no alternative intervention acceptable to the parents that is likely to prevent serious and irreversible harm to the child.[39] Thus, the crucial moral question with regard to a parental request for genetic testing for their child is whether such testing poses the likelihood of serious and irreversible harm to the interests of the child.

There are clearly circumstances in which genetic testing for inherited cancer susceptibility has established medical benefit for children.[40] For example, in families with a history of retinoblastoma, testing of infants for the *RB* gene serves two important functions. For children who test positive, regular eye examinations may provide for early diagnosis and treatment of the disease, possibly with full preservation of eyesight. For children without the inherited predisposition, the discomfort of frequent eye exams can be avoided. Similarly, in families with FAP, affected children may develop cancerous polyps before puberty, so surveillance with colonoscopy is crucial to the timing of surgical interventions to avoid the spread of untreatable disease. Thus, genetic testing to determine whether children have inherited the mutation and require aggressive monitoring is essential to maintaining their health. In these cases, the moral right of parents to request such testing is not limited.

However, testing of children for inherited cancer susceptibility has no established medical benefit in most cases. For example, in families with *BRCA1* and *BRCA2* mutations breast and ovarian cancer do not occur until adulthood. There are no preventive lifestyle changes, monitoring regimens, or prophylactic interventions that are thought to facilitate risk reduction or early diagnosis for children with inherited susceptibility to breast and ovarian cancer. When there is no established medical benefit associated with testing, then the question of whether testing also poses the risk of serious and irreversible harm to the interests of children becomes paramount. If such risks are created, then the autonomy of parents to request such testing may be overridden to protect the interests of children.

There are good reasons for maintaining that testing may seriously undermine the interests of children when there is no established medical benefit. First, the psychosocial welfare of children may be seriously endangered.[41–43] The potential consequences of positive test results include creating emotional stress for children, inhibiting the completion of important developmental tasks, and inducing patterns of parenting that exacerbate these problems. With regard to emotional stresses, children may experience the same negative reactions as adults, such as anger, depression, and loss of self-esteem. These affective states may impair the ability of children to prepare for adult roles by making them less motivated to pursue highly challenging educational or occupational goals. They may also impair their ability to form healthy personal relationships. For example, feelings of unattractiveness or unworthiness may impede the development of romantic relationships, and worries about the health of future children may create ambivalence about assuming the role of parent. Finally, positive test results may induce deleterious patterns of parenting, causing parents to become overprotective, lower expectations for their children, provide them with less socialization to future roles, and treat them in ways unjustifiably different from unaffected siblings. Second, testing of children impairs the exercise of their own developing autonomy. Specifically, children have an interest in the preservation of their autonomy to decide about genetic susceptibility testing as adults, rather than hav-

ing the choice imposed on them as children.[44,45] As suggested earlier, individuals may assign different weight to the potential benefits and harms associated with genetic testing for cancer susceptibility. Moreover, persons have different values and goals about seeking and using predictive medical information in planning their lives. Testing of children in the absence of established medical benefit deprives them of the opportunity to decide for themselves whether susceptibility testing comports with the values and goals that they cherish as adults. Third, testing of children for inherited cancer susceptibility may impair their future opportunity. Reasonable opportunity to pursue their life plans as adults requires that children have continuing access to certain basic goods as they enter adulthood, such as higher education, desirable positions of employment, and adequate healthcare (via insurance). At present, there are insufficient legal protections to guarantee that children who test positive for adult-onset cancer susceptibilities will not be deprived of these basic goods when they enter adulthood. Thus, in the absence of established medical benefits the request of parents to have their children tested for inherited cancer susceptibility should not be satisfied by healthcare providers due to the potential for serious and irreversible harm to the relevant interests of children.

Additional issues about the limits of personal autonomy rights arise with regard to prenatal testing of fetuses and preimplantation assessment of embryos for inherited cancer susceptibility. Members of families with a history of inherited cancer may consider it highly desirable to avoid having children to whom they might transmit the susceptibility to cancer. Prenatal or preimplantation genetic assessment may enable them to have their own biologic children while avoiding transmission of this genetic risk. From a legal standpoint, the permissibility of using testing to guide selective abortion or selective implantation of embryos is clear. As long as Roe v Wade is not revised, states may not impose limits on the indications for which persons may choose abortion, provided that the fetus has not reached the stage of viability.[46] This same discretion under the privacy provisions of the US Constitution should apply to the selection of embryos for implantation. Thus, the only potential barrier to prenatal testing of fetuses or preimplantation testing of embryos is the willingness of healthcare providers to offer these genetic services.

The appropriateness of offering genetic testing of fetuses or embryos for inherited cancer susceptibility depends on whether there are risks of serious and irreversible harm to fetuses or embryos that should place limits on the autonomous choices of persons to request such testing. One issue here concerns whether fetuses and embryos have a moral status that even admits assignment of morally significant interests that might outweigh reproductive autonomy. If they possess the same moral status as adults, then selective abortion or selective discarding of embryos based on an inherited cancer susceptibility clearly violates their interest in preservation of life.[47] On the other hand, if embryos and fetuses are not assigned moral status, or if they have a moral status that is less weighty than that of children and adults, then testing them for inherited cancer susceptibilities may not involve the violation

of morally significant interests that might outweigh reproductive autonomy.

A second issue concerns whether there are limits on the conditions for which prenatal or preimplantation testing is appropriately offered.[48] Conditions for which testing is requested may include severe congenital anomalies, minor medical conditions like predisposition to moderate obesity, or even physical traits like eye color. Assuming that fetuses and embryos have some degree of moral standing and interests that merit consideration, it seems inappropriate to offer genetic testing leading to selective abortion or selective discarding of embryos to avoid trivial medical conditions or merely undesirable traits.[49,50] If a line must be drawn between appropriate and inappropriate indications for selection of fetuses and embryos, then it must be determined on which side testing for inherited cancer susceptibility resides. The answer to this question will obviously depend on the means available to reduce the adverse consequences of the inherited susceptibility. If the adverse consequences associated with the inherited cancer susceptibility can be controlled in a manner that allows persons to pursue their life plans in a satisfactory manner, then it would be difficult to justify the claim that selective abortion of fetuses or selective discarding of embryos does not pose a serious and irreversible harm to their interests. On the other hand, if inherited cancer susceptibility is viewed as a condition, like severe congenital anomalies, that itself imposes irremediable and severe harm on a person, then selective abortion or selective discarding of embryos does not constitute the imposition of a serious and irreversible harm on fetuses or embryos.

At present, both issues remain unresolved. There is no general agreement on the moral status of fetuses or embryos. Likewise, there is no general agreement regarding the indications for which it is appropriate to use genetic testing to facilitate selective abortion or selective discarding of preimplantation embryos. In light of these disagreements and the permissibility of these activities under law, the selection of fetuses and embryos on genetic grounds related to inherited cancer susceptibility appears to be a permissible component of the procreative liberty of individuals.[51]

Fair Treatment in Testing

Persons have a paramount interest in just or fair treatment vis à vis other individuals with respect to the distribution of goods and services in society. Criteria for fair distribution depend on the nature of the goods and the activity or practice in which the distribution is embedded. For example, fairness in athletic competitions requires that trophies be distributed to those whose performance is superior to their competitors. Fairness with respect to the provision of luxury consumer goods, like expensive cars or television sets, involves distribution according to the ability of persons to pay for such goods. By contrast, it is widely accepted that fairness in the distribution of basic or essential goods—those necessary for persons to pursue their life plans—should

occur in a manner that provides all persons with equal opportunity vis à vis one another.[52] For example, a basic education is crucial to the efforts of persons to achieve important goals in life. Social arrangements are considered unjust if members of one group are provided with less opportunity to be educated than members of other groups. This situation might occur when significantly less funding for public education is provided for schools in which students of one ethnic group predominate compared to schools populated primarily by members of another ethnic group. Concerns arise about the fairness of current social arrangements in which persons with inherited cancer susceptibility may not have access to important goods such as insurance and employment. The fundamental moral issue concerns which criteria of fair distribution apply to these goods and what implications follow for securing access by persons with inherited cancer susceptibility

A major focus of concern relates to the availability of health insurance and the access that it provides to adequate healthcare. Among Americans who have health insurance, nearly 80% participate in large-group plans in which the insurability of individuals is not assessed.[13] However, for persons seeking private healthcare insurance positive results of genetic testing for cancer susceptibility may be used to deny coverage, specify pre-existing conditions, increase rates, or set special claims limits. Even for persons who participate in small-group plans or who work for large self-insured employers, individual health profiles may be used to determine rates or establish claims limits, even if this information is not used to determine eligibility for health insurance.

Legal statutes addressing the access of affected individuals to health insurance provide only limited and uneven protection.[53] At the federal level, the Health Insurance Portability and Accountability Act of 1996 prohibits group health insurance plans from using genetic information to specify pre-existing conditions or determine eligibility for coverage, although the Act does not set restrictions on using this information to increase rates, set lifetime limits on coverage, or to establish other policy limitations.[54] With regard to state law, more than half of the states prohibit insurers from using the results of genetic tests to deny coverage or charge higher rates.[55] However, an important gap in these requirements was created by the federal Employee Retirement Income Security Act of 1974, which excludes employer initiated self-insurance health plans from the requirements of state insurance regulations. As a result, the question of whether the principle of justice requires restrictions on the access of health insurers to genetic information continues to have particular relevance.[56]

An argument can be mounted that fairness in access to health insurance or the contractual terms under which it may be purchased by persons with inherited cancer susceptibility should be based on their actuarially determined risk. First, if possession of an inherited cancer susceptibility cannot be used in determining insurance eligibility, rates, and limits of coverage, then low-risk unaffected persons are unfairly forced to subsidize the costs anticipated for high-risk persons who have an inherited cancer susceptibility. Insurers would be forced to charge higher overall rates to low-risk persons than would be necessary if they

could distinguish between those with and without inherited cancer susceptibility.[57] Second, if the use of information about genetic risk status cannot be used to determine the terms of health insurance coverage, then persons with equally high risk status deriving from nongenetic conditions will be treated unfairly vis à vis those with inherited cancer susceptibility. Insurers will be legally permitted to charge higher rates for persons who have significant risks for poor health due to nongenetic conditions than for persons with genetic conditions and similar health risks. In this respect, information about inherited cancer susceptibility should function no differently than other kinds of medical information to which insurers are already allowed access.[58] Third, if use of genetic information by insurers is prohibited, then those who know they have inherited cancer susceptibilities will be able to purchase more comprehensive insurance to cover the probability that they will have unusually high medical expenses. The phenomenon is called "adverse selection." This outcome will exacerbate the unfairness to unaffected persons, whose insurance costs will be further increased by the expenses associated with the medical care of those with inherited cancer susceptibility.

On this view, access to health insurance is determined by risk status and the ability to pay for the insurance products available on the open market. Health insurance is treated as a consumer good somewhat like televisions sets or, perhaps more analogously, mortgages or personal loans, because the terms of the latter are determined by the risk profile of the borrower. However, health insurance is not analogous to general consumer items that play no essential role in facilitating the opportunity of persons. In the absence of access to affordable health insurance and adequate healthcare, persons may be thwarted in their effort to pursue their life plans. In this respect, the status of health insurance seems more akin to public education than consumer goods like television sets or luxury cars.

If health insurance is assigned a status as an essential good, then an argument can be articulated in support of the view that fair distribution of access to it should be determined according to different criteria of justice.[59] According to this view, society is obligated to provide all persons access to essential goods in a manner that assures that they have an equal opportunity vis à vis other individuals to pursue their life plans. When persons are disadvantaged through no fault of their own with regard to their ability to secure basic goods, then society must provide them with special assistance or protection to assure that their opportunities in life are equal to those of persons who are more fortunate. An example is the legal requirement for the provision of wheelchair access of disabled persons to public buildings. In the absence of these provisions, persons who are wheelchair bound would be denied educational or work opportunities available to persons who are able to walk. Similarly, persons with inherited cancer susceptibility may be viewed as having a special vulnerability, through no fault of their own, that may result in the denial of access to basic goods like health insurance. If society is to assure that they possess equal opportunity compared to persons without these inherited traits, then special

protections must be established that deny insurers access to information about inherited cancer susceptibilities that might be used to determine eligibility for insurance or set highly unfavorable contractual terms.[60] Thus, fair distribution of health insurance considered as an essential good requires that it be distributed according to the criterion of equal opportunity.

Even if the status of health insurance as an essential good is granted, questions remain about the fairness of singling out inherited cancer susceptibility or other genetic conditions for special protection. An objection is that the sweep of the above argument is too broad. If the equal opportunity criterion for just distribution is applied to access to health insurance for persons with inherited cancer susceptibility or other genetic conditions, then it must also be applied to persons with nongenetic health conditions that may also result in denial of access to health insurance. This result is problematic because it would sweep aside actuarial risk assessment as a basis for determining eligibility for and the contractual terms of individual health insurance.

One response is to attempt to draw a distinction between medical conditions for which persons are not responsible and those resulting from lifestyle choices for which persons are responsible. While society may have an obligation of justice to repair inequalities of opportunity in access to basic goods for which persons are not responsible, it is not obligated to correct inequalities of access that result from the voluntary decisions of persons that compromise their ability to pursue their life plans.[61] Because inherited conditions are paradigm instances of conditions for which persons are not responsible, special assistance is appropriate to assure that these conditions do not impair the access of persons to basic goods. One problem with this response is that it assumes that we can easily distinguish between medical conditions for which persons are responsible and those for which they are not. More importantly, this response ignores the fact that there are many medical conditions unrelated to inherited traits, such as injuries resulting from unavoidable accidents, for which persons are not responsible. Therefore, the problem of why persons with inherited conditions should be singled out for special protections remains unresolved.

The most direct response to the objection is to admit that the argument in favor of special protections for access of persons with inherited cancer susceptibility is indeed overly broad, but that the objection itself cuts two ways. We might reject the equal opportunity criterion for fair distribution of access to health insurance because it would sweep aside the ability to determine access based on the risk assessment of individuals. Or, we might conclude that fair distribution according to the equal opportunity criterion requires that persons with nongenetic medical conditions be treated in precisely the same manner as persons with genetic conditions. In this case, individual risk rating must be considered unjust. To implement the equal opportunity principle, it is necessary to assure that all individuals have ready access to minimally adequate health insurance, either through government-sponsored programs or through privately administered insurance plans based solely on community rating mechanisms.

Persons with inherited cancer susceptibility might be denied access to other important forms of insurance as well, such as life and disability insurance. Criteria for the just distribution of access to these goods depends on whether they are conceptualized as general consumer items or as essential goods integral to the ability of persons to pursue their life plans. If the latter, then a similar argument can be constructed that the principle of equal opportunity should also guide access to these other forms of insurance as well. However, these goods are in general viewed as less essential to the ability of persons to pursue their life plans than access to healthcare, a basic education, or employment. Despite their being less essential, the absence of some minimally adequate amount of life insurance and disability insurance may arguably be claimed to impair the ability of persons to pursue their life plans. For example, lack of access to life insurance may thwart their goal to provide some security for their children in the event of their untimely death. Perhaps the most satisfactory solution regarding these other forms of insurance would be to legally prohibit the use of information about inherited cancer susceptibility with respect to the purchase of policies below a relatively modest amount. Nevertheless, this type of proposal is subject to the same charge of being overly broad that was made with respect to health insurance. If legal restrictions are placed on the access of insurers to information about inherited cancer susceptibility for life and disability insurance policies below a certain amount, then it is unclear why similar restrictions on the use of information about other medical conditions should not also be established.

Persons with inherited cancer susceptibility may also face denial of access to employment opportunities. Employers may be concerned about the potential costs posed by employees who are at increased risk for the development of serious, life-threatening illnesses. These costs include lost work time, the expense of training replacement employees, and, of course, healthcare claims. In the case of inherited conditions, substantial healthcare costs might also be incurred by dependent family members covered by employee group plans. Thus, employers have significant motivations to deny employment to persons with inherited cancer susceptibilities, restrict their opportunities for advancement, or not retain them.

The determination of the appropriate criteria for fair treatment of persons seems more straightforward with regard to employment opportunities. The opportunity to seek and retain gainful employment is fundamental to the ability of persons to pursue their life plans. Gainful employment is an essential good. As an essential good, justice requires that access to gainful employment should be distributed in a manner that persons have equal opportunity vis à vis other individuals. In this context, equal opportunity must be understood to mean that there should be no restrictions on the ability of persons to seek and retain specific positions of employment, except those restrictions related to their ability to actually perform the tasks associated with these positions. Because inherited cancer susceptibility does not in itself impair the ability of persons to perform specific job-related responsibilities, it follows that any restrictions in access to

employment based on this consideration represents morally unfair discrimination.

While the general principle that just distribution in access to employment should be conditioned only on ability to perform job-related tasks has been broadly recognized in law, there are significant gaps and deficiencies that render the legal protection for persons with inherited cancer susceptibilities relatively incomplete.[62] Only a handful of states prohibit employers from conducting genetic tests on job applicants or employees, or using the results of such tests in making employment decisions.[63] On the federal level, the Americans with Disabilities Act (ADA) prohibits employment discrimination against qualified persons in any aspect of employment based on their disabilities.[64] To qualify for protection under the ADA, persons must be able to perform the essential functions of the job, with or without some reasonable accommodation made by the employer, and must satisfy the definition of a person with a disability. The latter definition involves three disjunctive parts. The first two focus on persons who are either impaired in one or more major life activities or have a record of such impairment. Neither condition would apply to persons with an inherited cancer risk because they do not suffer from any impairment in major life activities, such as seeing, hearing, walking or speaking. The third condition specifies that persons qualify for ADA protection if they are regarded as impaired by the employer. Persons who are denied employment opportunities because they are considered a poor health risk, based on the determination that they have an inherited cancer susceptibility, might reasonably qualify as being regarded as impaired by an employer. However, the ADA does not specifically address the status of having an inherited susceptibility to disease. In 1995, the Equal Employment Opportunity Commission, the government agency that enforces the employment sections of the ADA, issued a written opinion that persons who are denied employment opportunities because of genetic predispositions are being regarded as disabled by employers and therefore qualify for protection under the ADA.[65] The merits of this opinion have not been tested in any court case, so the extension of the protections of the ADA to persons with genetic predispositions like inherited cancer susceptibility remains unsettled. Thus, implementation of the moral principle of justice as equality of opportunity in access to basic goods remains an unfinished project with regard to persons with inherited cancer susceptibilities.

Conclusions

The development and implementation of the capability to test persons for inherited cancer susceptibility will broadly transform the practice of clinical medicine in the coming years. This exciting new capability raises significant moral issues regarding the risk–benefit assessment of testing, the requirements and limitations of the autonomy of individuals in decision making about testing, and the fair treatment of persons with inherited cancer susceptibilities in access to important goods like health in-

surance and employment. The resolution of many of the moral issues is complicated by the current limitations and rapidly changing contours of our medical knowledge regarding inherited cancer. As new susceptibility genes are identified, these same limitations will recur and initially plague our efforts to resolve the moral issues as they pertain to specific types of inherited cancer susceptibility. As a result, the understanding of how the pertinent moral issues should be resolved must remain a work in progress. The preceding analysis is intended to provide a useful conceptual framework for addressing these moral issues as they arise with regard to particular inherited cancer susceptibilities.

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Genes and the Law

Darryl S. Weiman

With the Human Genome Project (HGP) nearing completion we are faced again with a situation where science has gone beyond what the legal system is prepared to deal with.* "[O]ur genes represent the most personal, private, and fundamental aspects of ourselves. They are inescapable; they cannot be concealed, disguised, or avoided. They are the ultimate identification and definition of who we are. . . . Research efforts like the Human Genome Project are unlocking the secrets of our genes on an almost daily basis."[1] The potential for abuse of genetic information is far-reaching, and in fact, some state legislatures and U.S. Congress have taken steps to prevent this abuse.† Genetic discrimination in the workplace and in obtaining insurance are obvious areas of concern that have yet to be adequately addressed by legislatures. Also, the issues of privacy—does an individual have a right to protect his individual genome, or should it be made available to other parties—have yet to be defined. Last, there will be an impact of genetic testing on the family: Intrafamilial relationships and future generations may be profoundly affected. The following is a brief overview of the potential problems facing insurers and the insured, the possibility of genetic discrimination in the workplace, and the dilemma facing healthcare providers, who may not know what to do with the genetic information as it becomes available. Past legislative efforts to deal with the potential problems of genetic testing will be reviewed and future legislative trends discussed.

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*The HGP is an international project that began in October 1990 and is now essentially complete. The goal of the project was to discover all of the 60,000 to 80,000 human genes (which make up the human genome) and map them so that further research on the human genome could be readily done.

†At least 19 states have enacted laws to restrict how genetic information is used in the health insurance industry, and at least 31 states have laws prohibiting genetic discrimination in insurance.[2]

Insurers Must Have Access to Genetic Information for Fair Underwriting

The insurance industry is by necessity discriminatory. Individuals who have a higher risk of getting diseases and/or a higher risk of dying are routinely charged a higher premium or are turned down for insurance altogether. Under a principle of equity (which should not be mistaken for equality), insureds who have the same or similar actuarial risks are charged the same premium. The higher the risks, the higher the premiums. The goal of the equity system is to have each insured pay a premium indicative of the risk facing that individual.*

Currently, insurance companies use data such as age, sex, medical history, current health status, risk behavior (such as smoking or skydiving), and occupation along with physical exams and certain blood work and other diagnostic tests (electrocardiogram and chest radiograph) to get a risk classification on an individual. With the results of the HGP, insurers are going to need the information available from genetic testing to derive the proper risk stratification for the system to work. The danger to the insurer is twofold: If the insurer is too low in the risk assessment, it will not have enough funds to pay for the claims that it is contractually obligated to pay. In this scenario, the insurer will go bankrupt. If the insurer charges too high of a premium, the free market should drive the insured to another company that has lower premiums, and again, the insurer is in danger of being driven out of the business.

In the current system of insurance, the applicant has an obligation to disclose relevant information so that the insurer can make a fair risk assessment. If the applicant has access to genetic information that would not be available to the insurer, the insurer would be at risk of assigning too low of a premium and thus would not be able to cover the applicant's future claims. "An applicant's bad faith non-disclosure is tantamount to fraud against the insurer and other policy holders. The result is that the equity rationale—the principle of fair discrimination—underlying risk classification is violated if an insurer raises premiums for all policyholders to cover losses, unexpected from the insurer's standpoint, but expected by the applicant."[4]

Genetic Information Should Not Be Available to Insurers

Those who argue against making genetic information available to insurers point out that the information is not reliable or accurate. Because the information is not accurate, it cannot be used in forming a reasonable risk assessment for insurance purposes. Many do not want their

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*Premiums based on risk stratification allows most applicants to obtain insurance. For example, most insurers accept 70% to 80% of applicants for health coverage at standard rates. Less than 10% of applicants are turned down for insurance.[3]

genetic information to be shared for fear of stigmatization of those with genetic diseases both in the workplace or elsewhere.† Also, there are some who will not want to know what their genetic profile is for fear of what it might reveal.

The Fourth Amendment of the U.S. Constitution forbids unreasonable searches and seizures of person, property, and effects but will allow searches and seizures based on probable cause spelled out with particularity in a warrant. The warrant must be granted by an unbiased member of the judiciary.* The Fourth Amendment is applicable to the federal government, but its provisions are made applicable to the states under the Fourteenth Amendment.† Although the Constitution has no express provision stating that privacy is a right, the U.S. Supreme Court has interpreted this Amendment to imply that right under certain circumstances. In *Katz v United States*, the Court held that if a person expresses an expectation of privacy, that expectation will be honored if the public deems that expectation to be reasonable under the circumstances. "One of the most cherished, basic, and vital human rights is the right to privacy, the long-standing American 'right to be let alone.' "[5] Each person's genome can be thought of as that person's personal property, but society (the Court or Legislature) has not yet decided if the expectation of keeping that information private is "reasonable."

Even if the Court decides that an individual's genome is private information, there is nothing under the Constitution keeping private interests from demanding that information. Insurance companies routinely require confidential medical information prior to awarding a policy. Employers often inquire into private medical information prior to offering a job. Disclosure of an individual's genetic profile could have far-reaching effects. ". . . [U]nlike a discrete transient illness or disease, a genetic disease, disorder, or condition is immutable. An inappropriate disclosure of genetic information may stigmatize an individual for life, causing serious emotional, financial, and perhaps physical harm."[6,7]

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†Employers may not want to hire someone who is likely to develop a cancer or die of heart disease in the near future. Also, students with genetic diseases may be denied student loans for concerns of their ability to pay off these loans in the future. The same reasoning can be used for those applying for mortgages when buying a home—mortgagees may require a genetic screen to assess the risk of dying for those who are applying for the loan.

*The Fourth Amendment states "[t]he right of the people to be secure in their persons, houses, papers, and effects, against unreasonable searches and seizures, shall not be violated, and no Warrants shall issue, but upon probable cause, supported by Oath or affirmation, and particularly describing the place to be searched, and the persons or things to be seized."

†The Fourteenth Amendment states " . . . [n]o State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws.

Genetic Information May Lead to Discrimination in the Workplace

Impact of Genetic Testing on the Family

Mandated genetic testing has been tried in the past. In the 1970s, laws were passed in some states to perform genetic testing on African-Americans to look for carriers of sickle cell anemia. If two carriers of the disorder were to get married, the chance of one of their offspring getting the disease was one in four—reproductive planning would be based on the knowledge. Counseling was not provided, and as a result, couples did not know what to do with the information. Insurance carriers and employers also did not know what to do with the information, and as a result, healthy carriers of the trait were discriminated against.[8]

Genetic information given freely to individuals may have harmful psychological effects. " . . .[p]sychologic harms resulting from genetic information abuses include: anxiety caused by inaccurate testing; a stigmatic effect; and harm caused by revealing information about an individual's immutable genome, in a sense, their mortality."[9]

If people are given disheartening genetic information, they may make life-changing decisions regarding marriage, reproduction, education, and employment. These decisions may not be justified, because many genetic diseases are multifactorial, and it is uncertain when or if the disease will ever become manifest.

Many diseases are multifactorial. A gene that predisposes a person to developing some disease process may not be expressed if the appropriate environmental stimuli are avoided. If such a gene is discovered, steps can be taken to minimize the risk of disease development if that person is appropriately counseled. If counseling is not available, the individual may not know what to make of the information. Stress and anxiety and, in some instances, poor decision making may result. Health professionals must arm themselves with the information necessary to counsel their patients so that wise decision making can be done with this new information. The mistakes of the sickle cell anemia project should not be revisited.

Legislative Attempts to Regulate Dissemination of Genetic Information

Should genetic information be regulated on the federal level (by an act of Congress), the state level, or should it be left alone and let the free market forces work it out? Because genetic information can affect every citizen, and Congress has the power to regulate business that affects a public interest under the Commerce Clause of the Constitution, it seems that a national solution would be optimal.* However, regulation

*Under the Commerce Clause, Congress has the power "[t]o regulate Commerce with foreign Nations, and among the several states, and with the Indian Tribes."

of the insurance industry has been historically left to the states. An attempt to regulate insurance at the federal level was tried in 1905, but this bill in the US Senate was defeated. Louis D. Brandeis, later to become a Supreme Court justice, was counsel for the Protective Committee of policy holders in the Equitable Life Assurance Society. "The sole effect of a Federal law would be . . . to free the companies from the careful scrutiny of the commissioners of some of the States. It seeks to rob the State even of the right to protect its own citizens from the legalized robbery to which present insurance measures subject the citizens . . ." (United States v South-Eastern Underwriters Association, 322 US 533, 594 n.17 [J. Jackson dissenting in part] [quoting Louis D. Brandeis, address before the Commercial Club of Boston, October 1905], rehearing denied, 323 US 811 1944). The South-Eastern decision gave Congress the go-ahead to regulate the insurance industry, but a concerted lobbying effort by the states led to the passage of the McCarran-Ferguson Insurance Act of 1945. This Act gave the states the power to regulate the insurance industry but reserved the power of the Congress to enact legislation relating to the business of that industry.

In 1974, Congress passed the Employee Retirement Security Act (ERISA) in an effort to protect employees and their beneficiaries in employee benefit plans. Unfortunately, ERISA does not regulate self-insured plans, which are also free from state regulation. Also, ERISA holds that the states are not allowed to deem an employee benefit plan to be an insurance company. The effect of ERISA is to allow employers who self-insure to be free of regulation by state insurance commissioners. The employer does not have to maintain minimum health benefits, and they do not have to pay insurance premium taxes, which would be used to maintain high-risk insurance pools. The self-funded employer may change health insurance benefits as it sees fit. Of course, this affords no protection to the employee, who may be forced to undergo genetic testing, and who may face loss of coverage for any genetic condition that may be found.

"One point is clear. The extent to which self-funded plans will cover employees is, with ERISA's blessing, at the absolute discretion of the employer. Moreover, an employer's power to limit or exclude employee health insurance benefits under conditions solely determined by the employer has been upheld in the context of medical coverage for AIDS under an employer's self-insured plan. When considering this power to self-regulate together with the financial incentives employers have to reduce cost of health care, it is reasonably foreseeable that employers will pragmatically use genetic information following completion of the HGP to make decisions about health insurance coverages."[10]

In *McGann v H&H Music Co*, 946 F2d 401 (5th Cir. 1991), the Fifth Circuit held that an employer was legally within its rights when it reduced the maximum benefit level of insurance of one of its employees (who had acquired immunodeficiency syndrome) from $1 million to $5,000. This does not bode well for employees who may be faced with genetic testing.

In 1990, Congress passed and President George H. Bush signed into law the Americans with Disabilities Act (ADA). This Act was designed

to give individuals with disabilities protection from discrimination in the workplace. Although there is no explicit mention of genetic discrimination in the Act, the ADA has broad language that clearly includes individuals who have a clinically manifest genetic illness that substantially limits their ability in performing a major life activity.* The ADA requires that employers must make reasonable accommodations for qualified individuals with disabilities so long as those accommodations do not cause an unreasonable hardship on the employer.

Although the ADA protects those with a manifest genetic disability, the question remains as to whether the ADA applies to a genetic predisposition that has not yet occurred. In 1995, the Equal Employment Opportunity Commission (EEOC) ruled that the ADA covers asymptomatic workers with a genetic disorder that has not yet become clinically present. The EEOC reasoned that employers who would discriminate based on genetic information relating to illness and disease are actually "regarding" the individual as being impaired. Under the "regarded as" prong of the ADA, these individuals would be considered as impaired to a level that would substantially limit a major life activity—it affects their ability to compete for or maintain employment. It is important to realize that even though the EEOC guidelines can be used to interpret the law, they do not have the force of law as would a federal or state statute. A person who has a genetic trait that has not yet become clinically manifest must prove that they were "regarded as having such an impairment" by the employer and must also prove that the employer discriminated against them based on this perception.

Even though the EEOC states that the ADA protects persons who have genetic conditions that have not yet become clinically manifest, it is uncertain that the courts will follow this line of reasoning. Would it be fair to consider a person as disabled if he is the carrier of a gene that may lead to a cancer in the future? What if the gene only predisposes to a disease that may never become manifest so long as environmental factors are controlled?

The ADA does not prohibit genetic testing. Employers may use genetic testing so long as they can show that the testing is job related and consistent with a business necessity. The testing cannot single out individuals and must be given to all employees; and, the knowledge gained from the tests could be used to improve the work environment for the employee involved. Of course, there is potential for abuse with this testing, and there need to be safeguards in place to prevent this potential abuse.

Privacy and the Medical Record

Historically, release of medical information required the consent of the patient or his family. The George W. Bush administration has proposed

*The ADA defines a person with a disability as one who has one or more physical or mental impairments that substantially limits him/her in performing a major life activity, a person with a record of such impairment, or a person who is regarded as having such an impairment.

to change the rules by eliminating the patient consent requirement before their doctors, hospitals, or pharmacies use or disclose the information.[11] These new rules may

> " . . . create a loophole allowing companies that administer their own health plans to avoid putting up a firewall between employees health data and their employment records, making it easier for employers to snoop into a worker's health problems" (Janlori Goldman, director of the Health Privacy Project at the Institute for Health Care Research and Policy at Georgetown University).

There is now the obvious risk that employers may use the information inappropriately, such as in deciding who to hire and who to fire.

Conclusions

With the completion of the HGP, research into human diseases that have a genetic component may soon lead to new therapies for cancer, cardiovascular diseases, congenital defects, and other medical disorders. There is, however, a downside to this newfound knowledge as the possibilities of discrimination in the workplace, discrimination in the ability to obtain insurance, and uncertainty with what to do with medical information for which medical treatment is not yet effective or available becomes manifest. Congress and state legislatures are aware of the potential problems and efforts are ongoing to solve these problems.

It will be interesting to see how congressional hearings play out as our legislators strive to maximize the benefits to be derived from new genetic information while at the same time minimize the risk of abuse of that information.

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5

Breast Cancer Genetics

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The goal of breast cancer research is to reduce the morbidity and mortality associated with the disease. This can be achieved either by cure of existing cancer or prevention of new cases. Cure rates are enhanced when breast cancer is diagnosed at an early stage and when therapies are applied according to clearly defined indicators. The problem being confronted is enormous. In the United States, an estimated 203,500 women will have been diagnosed with breast cancer in 2002, and 40,000 will die from the disease (Tables 5.1 and 5.2).[1] Breast cancer progression is the result of a multistep process in which the cumulative effect of successive discrete genetic alterations leads to a gradual transition from normal through premalignant to frankly malignant tissue and ultimately to metastasis.[2] Our understanding of breast cancer biology continues to increase through the characterization of the genes involved in this progressive transformation.[3–7] Much of this knowledge is derived from studies of the alterations that occur in breast tumor cells and from studies of families with inherited susceptibility to breast cancer.[3–12] Our increasing knowledge provides many opportunities for intervention, including increased surveillance of populations at risk, institution of chemoprevention therapy (tamoxifen) for patients at high risk of disease (genetic predisposition, prior breast cancer) as well as for patients with preinvasive lesions (carcinoma in situ), and specific therapy for early stage invasive cancer based on specific prognostic and predictive indicators. Even for advanced breast cancer, knowledge of the genetic abnormalities underlying a cancer's progression can impact patient well being and survival (e.g., *HER2/neu* overexpression).

Because breast cancer has been termed a genetic disease, it is easy to assume that any woman with a positive family history who develops breast cancer has done so because of an inherited predisposition. In fact, only 20% to 30% of all women who develop breast cancer report a positive family history, and not all of these women have hereditary susceptibility to the disease.[13–15] Several nongenetic factors can lead to familial clustering of breast cancer, including: (1) a large family in which many women reach old age, and chance alone causes multiple women to develop this common cancer; (2) an extended family

Table 5.1 Age-specific breast cancer incidence rates by race per 100,000 US population.

Age at diagnosis	Caucasian	African American	Overall
20–24	0.9	1.7	1.0
25–29	7.4	11.1	7.8
30–34	25.0	32.3	25.6
35–39	63.1	68.6	63.6
40–44	127.1	134.9	126.9
45–49	203.6	176.3	198.3
50–54	238.4	209.0	228.9
55–59	285.6	235.4	274.8
60–64	364.2	287.4	348.3
65–69	430.0	326.0	412.1
70–74	468.5	335.6	450.3
75–89	502.5	366.5	483.9
80–84	490.7	379.0	477.1

Source: Adapted with permission from Reis LAG, Miller BA, Hankey BF, et al., eds. SEER Cancer Statistics Review, 1973–1991: Tables and Graphs. NIH Pub. No. 94-2789. Bethesda, MD: National Cancer Institute; 1994.

living in the same geographic location with exposure to similar environmental carcinogens; (3) culturally motivated behavior that may alter risk factor profiles such as age at first live birth and breastfeeding practices; and (4) socioeconomic influences that might result in differing dietary exposures.[16] Finally, the multiple but unclassified genetic factors that indirectly influence the development of breast cancer in any one individual are likely to be shared among genetically similar members of an extended family.[17]

There is confusion about the difference between "inherited" or "hereditary breast cancer" and "familial breast cancer." Inherited or hereditary breast cancer refers to breast cancer associated with a known or suspected high-penetrance gene mutation.[16] Familial breast cancer, on the other hand, refers to clusters of breast cancer in a given family that do not appear to result from chance alone but do not fit the stricter criteria for inherited breast cancer. Familial breast cancer also tends to have a later age at onset and affects fewer persons in the family than hereditary breast cancer.

Only 5% to 10% of breast cancers appear to be caused by inheritance of high penetrance mutations in breast cancer susceptibility genes, which are inherited in an autosomal dominant fashion (Table 5.3). These include mutations in genes such as *BRCA1*, *BRCA2*, *p53*, and *STK11/LKB1*, which account for the majority of all inherited breast can-

Table 5.2 Age-specific breast cancer incidence rates (%) by age.

Current age (yrs)	Breast cancer incidence by age (yrs)			
	50	60	70	80
30	1.99	4.29	7.47	10.57
40	1.58	3.91	7.13	10.28
50	—	2.41	5.74	9.01

Source: Adapted with permission from Feuer et al.[50]

Table 5.3 Percent incidence of breast cancer causes.

Sporadic breast cancer	65–75%
Familial breast cancer	20–30%
Hereditary breast cancer	5–10%
*BRCA1**	~45%
BRCA2	~35%
p53 (Li-Fraumeni syndrome)	~1%
STK11/LKB1 (Peutz-Jeghers syndrome)	<1%
PTEN (Cowden's disease)	<1%
MSH2/MLH1 (Muir-Torre syndrome)	<1%
ATM (AT)	<1%
Unknown	~20%

*Affected gene.

cers.[13–15,18–23] Recent identification of these dominant mutations makes it possible to offer predictive DNA testing to those at high risk for breast cancer. Much remains to be understood concerning other high-penetrance gene mutations, as well as genetic polymorphisms or low-penetrance gene mutations that influence individual response to environmental carcinogens.[22–25] Research into breast cancer genetics is providing new insights into the etiology of breast cancer, which are being translated into methods for earlier diagnosis and better treatment strategies for the entire population of women with breast cancer.

An intensive effort to define prognostic biomarkers for breast cancer is also underway. Candidate biomarkers include indices of proliferation such as proliferating cell nuclear antigen (PCNA), bromodeoxyuridine (BrUdR), and Ki-67; apoptotic indicators such as bcl-2 and the bax/bcl-2 ratio; indices of angiogenesis such as vascular endothelial growth factor (VEGF) and the angiogenesis index; growth factor receptors such as EGFr and *HER2/neu*; and *p53*. Finally, our management of breast cancer patients is being complimented by translational research involving breast cancer angiogenesis and the *HER2/neu* oncogene. This chapter provides an overview of important developments in each of these areas with an emphasis on their clinical significance.

Risk Assessment

Breast cancer etiology is multifactorial and demonstrates the strong interplay of genetic and environmental factors. While one of the most important risk factors for breast cancer is a family history of the disease, many nongenetic risk factors contribute to its etiology. These nongenetic factors can be broadly categorized as hormonal and non-hormonal.

Hormonal and Nonhormonal Risk Factors

A prolonged or increased exposure to estrogen is associated with an increased risk for developing breast cancer, whereas reducing exposure is thought to be protective.[26–28] Correspondingly, factors that increase the number of menstrual cycles are associated with increased

risk such as early age at menarche, nulliparity, and late onset of menopause.[29–31] Moderate levels of exercise and a longer lactation period, factors that decrease the total number of ovulatory cycles, can be protective.[32,33] There also is evidence suggesting that older maternal age at first live birth is associated with an increased risk of breast cancer.[34] These data suggest a protective effect of the terminal differentiation of breast epithelium associated with a full-term pregnancy. This effect appears to be most protective at an early age. Finally, there is an association between obesity and increased breast cancer risk.[35,36] Because the major source of estrogen in postmenopausal women is from the conversion of androstenedione to estrone by adipose tissue, obesity is associated with a long-term increase in estrogen exposure.

Some nonhormonal risk factors are indirectly associated with estrogen exposure. One risk factor that is modified by the hormonal milieu is exposure to ionizing radiation. Young women who received mantle radiation for Hodgkin's disease have a markedly increased risk for breast cancer with an incidence ratio of 75.3:1 compared with age-matched control subjects.[37,38] In addition, survivors of the atomic bomb blasts in Japan during World War II have a high incidence of breast cancer, likely because of somatic mutations introduced directly by radiation exposure.[39] In both cases, it appears that exposure during adolescence, a period of active breast development, magnifies the deleterious effect of radiation exposure.[40,41] A number of studies have suggested that the amount and duration of alcohol consumption are also associated with an increased breast cancer risk.[42–44] Alcohol consumption is known to increase serum levels of estradiol.[45] Finally, evidence suggests that certain dietary factors, such as high dietary fat and "well-done" meat, also contribute to an increased risk of breast cancer.[46–49] Dietary fat intake can increase serum estrogen levels, and well-done meat contains specific fenotoxins.

Risk Assessment Models

The average lifetime risk of breast cancer in the US female population at birth is 12%, or approximately one in eight.[50] The longer a woman lives without cancer, the lower her risk of subsequently developing breast cancer. Thus, a 50-year-old woman has an 11% lifetime risk of developing breast cancer, while a 70-year-old woman has a 7% lifetime risk of developing breast cancer. Many studies have evaluated risk factors for breast cancer, but because these factors interact, evaluating the risk conferred by combinations of risk factors is challenging.[51–62] Risk factors that are less consistently associated with breast cancer (such as diet, use of oral contraceptives, lactation, and abortion) or are rare in the general population (such as radiation exposure) have not been included in risk assessment models.[57–62]

Two risk assessment models are frequently used to predict the risk of breast cancer. From the Breast Cancer Detection Demonstration Project, a large mammography screening program conducted in the 1970s, Gail et al. developed the most commonly used model.[55] This model incorporates the age at menarche, number of breast biopsies, age at first

live birth, and the number of first-degree relatives with breast cancer (Table 5.4). It predicts the cumulative risk of breast cancer according to decade of life up to age 90. To calculate breast cancer risk with the Gail model, a woman's risk factors are translated into an overall risk score by multiplying her relative risks from several categories (Table 5.4). The risk score is then multiplied by an adjusted population risk of breast cancer to determine the individual risk of breast cancer. A software program incorporating the Gail model is available from the National Cancer Institute at http://bcra.nci.nih.gov/brc.

The other commonly used risk assessment model was developed by Claus et al. on the basis of data from the Cancer and Steroid Hormone Study, a large, population-based, case-control study of breast cancer.[63] This model is based on assumptions of the prevalence of high-penetrance genes for susceptibility to breast cancer. As compared with the Gail model, the Claus model incorporates more extensive information about family history, but it excludes risk factors other than family history. On the basis of knowledge of first- and second-degree relatives

Table 5.4 Relative risk estimates for the Gail model.

Variable	Relative risk
Age at menarche (yr.)	
≥14	1.00
12–13	1.10
<12	1.21
No. of biopsies/history of benign breast disease, age <50	
0	1.00
1	1.70
≥2	2.88
No. of biopsies/history of benign breast disease, age ≥50	
0	1.02
1	1.27
≥2	1.62
Age at first live birth (yrs)	
<20	
No. of first-degree relatives with history of breast cancer	
0	1.00
1	2.61
≥2	6.80
20–24	
No. of first-degree relatives with history of breast cancer	
0	1.24
1	2.68
≥2	5.78
25–29	
No. of first-degree relatives with history of breast cancer	
0	1.55
1	2.76
≥2	4.91
≥30	
No. of first-degree relatives with history of breast cancer	
0	1.93
1	2.83
≥2	4.17

with breast cancer and their age at diagnosis, the Claus model provides individual estimates of breast cancer risk according to decade from ages 29 to 79.

Risk Management

Several important medical decisions may be affected by a woman's underlying risk of breast cancer.[64] These decisions include whether to use postmenopausal hormone replacement therapy (HRT), at what age to begin mammography screening, whether to use tamoxifen to prevent breast cancer, and whether to perform prophylactic mastectomy to prevent breast cancer (Tables 5.5 and 5.6).

Postmenopausal HRT reduces the risk of coronary artery disease and osteoporosis by 50% but increases the risk of breast cancer by only 30% to 40%.[65–67] Because the average woman's risk of dying from coronary artery disease is much greater than her risk of dying from breast cancer, it is argued that the benefits of HRT outweigh the risks.[68,69] However, the balance between the risks and benefits of HRT may shift for women who have a substantially increased risk of breast cancer. In one study, HRT no longer increased life expectancy for women with a lifetime breast cancer risk above 30% and an average risk of cardiac events. Although the number of postmenopausal women with such a high risk of breast cancer is small, assessment of breast cancer risk provides valuable information for use in making decisions about HRT.[51–53] Further, assessment of breast cancer risk may reassure the great majority of women with a risk below this threshold that the benefits of HRT outweigh its risks.

Routine use of screening mammography in women 50 or older reduces mortality from breast cancer by approximately one third.[70] This

Table 5.5 Screening and risk reduction recommendations for *BRCA* mutation carriers.

	Recommendation	Frequency
Breast	Screening	
	Mammography	Yearly beginning at age 25
	Breast examination	Every 6 mo beginning at age 25
	Breast self-examination	Monthly beginning at age 18
	Chemoprevention	
	Tamoxifen	Consider at age 35 and after completion of childbearing
	Surgery	
	Bilateral mastectomy	Consider as an option to screening ± tamoxifen
Ovary	Screening	
	Transvaginal ultrasound	Every 6 mo beginning at age 25
	Serum CA125	Every 6 mo beginning at age 25
	Chemoprevention	
	Oral contraceptives	Consider during childbearing years
	Surgery	
	Bilateral salpingo-oopherectomy	Consider at age 35 and after completion of childbearing

Table 5.6 Timing of new cancer diagnoses after *BRCA* mutation testing.

	Breast cancer			Ovarian cancer	
Timing	**DCIS**	**T1N0**	**T1N1**	**Stage I**	**Stage II**
At risk-reduction surgery*	10%†	—	—	10%	—
At scheduled screening clinic visit	15%	10%	5%	10%	10%
Between scheduled screening clinic visits	—	20%	10%	—	—

*Bilateral mastectomy and bilateral salpingo-oopherectomy.
†Percent of cases studied.
Source: Adapted with permission from Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. J Clin Oncol 2002;20:1260.

reduction comes without substantial risks and at an acceptable economic cost.[71,72] However, the use of screening mammography is more controversial in women under the age of 50, for several reasons. First, breast density is in general higher in younger women, and screening mammography is less likely to detect early breast cancer. Thus, the reduction in mortality from breast cancer is lower.[73] Second, screening mammography in younger women results in more false-positive tests, resulting in negative biopsies.[74] Third, women under the age of 50 are less likely to have breast cancer, and fewer women in this age group will benefit from screening.[75] However, on a population basis the benefits of screening mammography in women between ages 40 and 49 still appear to outweigh the risks.[76,77] Targeting mammography to women at higher risk of breast cancer can improve the balance of risks and benefits.[78–80] In one study of women ages 40 to 49, an abnormal mammogram was more than three times as likely to be associated with cancer in a woman with a family history of cancer as in a woman without a family history of cancer.[74]

Tamoxifen, a selective estrogen receptor modulator, is the first drug shown to reduce the incidence of breast cancer in healthy women. The Breast Cancer Prevention Trial randomly assigned more than 13,000 women with a 5-year risk of breast cancer of 1.7% or more to tamoxifen or placebo.[81] Tamoxifen, after a mean follow-up period of 4 years, had reduced the incidence of breast cancer by 49% as compared to placebo. Tamoxifen is currently the only drug approved by the Food and Drug Administration (FDA) for reducing the risk of breast cancer. Assessment of breast cancer risk is important in making decisions about tamoxifen for several reasons. First, the Breast Cancer Prevention Trial enrolled only women with a 5-year breast cancer risk of 1.7% or more, and it is unclear whether the benefits of tamoxifen apply to women at lower risk. It is recommended that only women whose risk of breast cancer is at or above this threshold use tamoxifen.[82] Second, the benefit analysis of tamoxifen that is currently available finds the higher a woman's risk of breast cancer, the more likely it is that serious side effects, including venous thromboembolism, endometrial cancer, and

cataracts, will occur. In women taking tamoxifen, deep venous thrombosis occurs 1.6 times, pulmonary emboli 3 times, and endometrial cancer 2.5 times as often as in control women. The increased risk for endometrial cancer is restricted to early-stage cancers in postmenopausal women. Cataract surgery is required almost twice as often among women taking tamoxifen.

A recent retrospective study of women at high risk for breast cancer found that prophylactic mastectomy reduced their risk by more than 90%.[83] However, prophylactic mastectomy involves extensive and disfiguring surgery and has nonquantified effects on the long-term quality of life.[84] Further, the reduction in risk achieved by prophylactic mastectomy depends on a woman's underlying risk of breast cancer. A study involving women who were carriers of *BRCA1* or *BRCA2* mutations found that the benefit of prophylactic mastectomy differed substantially according to the breast cancer risk conferred by the mutations.[85] For women with an estimated lifetime risk of 40% (approximately four times the population risk) prophylactic mastectomy added almost 3 years of life, whereas for women with an estimated lifetime risk of 85% prophylactic mastectomy added more than 5 years.

Genetic Risk Factors

Breast Cancer Susceptibility Genes

BRCA1

Five to 10% of breast cancers are caused by inheritance of germline mutations in breast cancer susceptibility genes such as *BRCA1* and *BRCA2*, which are inherited in an autosomal-dominant fashion with varying penetrance (Table 5.3). *BRCA1* is located on chromosome 17q, spans a genomic region of about 100 kb of DNA, and contains 22 coding exons. The full-length mRNA is 7.8 kb and encodes a protein of 1,863 amino acids. Both *BRCA1* and *BRCA2* function as tumor suppressor genes, and for each gene, loss of both alleles is required for the initiation of cancer. Data accumulated since the isolation of the *BRCA1* gene suggest a role in transcription, cell cycle control, and DNA damage repair pathways.[86–101]

Since the isolation of *BRCA1*, more than 500 sequence variations have been identified. Initially, eight disease-associated mutations were described within the gene,[102,103] followed rapidly by an increasing number of novel mutations.[104–106] Most sequence variations result from frameshift mutations, but several missense mutations are also known to alter protein function. Splice acceptor and donor sites are also frequently mutated. Several specific classes of mutations with important clinical implications have been described (Table 5.7). It is now known that germline mutations in *BRCA1* represent a predisposing genetic factor in as many as 45% of hereditary breast cancers and in at least 80% of hereditary ovarian cancers.[107–109] Female mutation carriers have a 60% to 90% lifetime risk for developing breast cancer and a 20% to 40% lifetime risk for developing ovarian cancer (Table 5.8).[110–112] Breast

Table 5.7 Characteristics of *BRCA1*- and *BRCA2*-associated breast cancers.

Characteristic	*BRCA1*	*BRCA2*
Gene locus and product	17q21, 1,863 amino acids	13q12–13, 3,418 amino acids
Incidence/penetrance of germline mutation	Germline mutations are highly penetrant, conferring a risk of about 90% for either breast or ovarian cancer by age 70	Germline mutations are predicted to account for nearly 35% of families with multiple-case, early-onset female breast cancer
Tumor spectrum	Female breast cancer, ovarian cancer, possibly colon and prostate	Female breast cancer, ovarian cancer, male breast cancer, colon cancer, prostate cancer, pancreatic cancer, gallbladder, bile duct, and stomach cancers, malignant melanoma
Genotype–phenotype correlation	The risks for breast and ovarian cancer are related to the position of the mutation, with truncating mutations in the first two thirds of the coding region being associated with a higher ovarian cancer risk, relative to breast cancer risk, than mutations in the last third	Truncating mutations identified in families with the highest risk of ovarian cancer relative to breast cancer are clustered in a region of approximately 3.3 kb in exon 11 bordered by nucleotides 3,035 and 6,629
Somatic mutations	Infrequent in primary breast and ovarian carcinomas	Infrequent in primary breast and ovarian carcinomas
Clinical and morphological characteristics of the primary breast cancers	Early age onset, high prevalence of bilateral cancer, estrogen receptor negativity, higher proliferative activity, poor histological differentiation, less frequent *HER2/neu* activation, lower frequency of nodal metastases, fewer recurrences, more favorable prognosis	Early age onset, high prevalence of bilateral cancer, lower proliferative activity, well-differentiated histological characteristics

Source: Adapted with permission from Ronai Z, Minamoto T. Early detection of gene mutation in cancer diagnosis. PPO Updates 2001;15(1):1.

cancer in these families appears as a classic mendelian trait of autosomal dominance with high penetrance. Approximately 50% of children of carriers inherit the trait. In general, *BRCA1*-associated breast cancers are invasive ductal carcinomas and are poorly differentiated and hormone receptor negative (Table 5.7). *BRCA1*-associated breast cancers have a number of distinguishing clinical features, such as an early age of onset compared with sporadic cases, a higher prevalence of bilateral breast cancer, and the presence of associated tumors in some affected individuals, specifically ovarian cancer and possibly colon and prostate cancers.[113–115]

Several founder mutations have been identified in *BRCA1*. The two most common mutations are 185delAG and 5382insC, which account for approximately 10% of all the mutations seen in *BRCA1*.[116] These two mutations occur at a 10-fold higher frequency in the Ashkenazi Jewish population than in non-Jewish Caucasians.[117,118] The carrier fre-

Table 5.8 Cumulative age-specific risk for breast cancer.

Age (y)	General population (%)	Women with *BRCA1* mutation (%)
40	<1	16
45	1	42
50	2	59
55	3	72
60	4	77
65	6	80
70	7	82
75	9	84
80	10	86

Source: Adapted with permission from King MC, Rowell S, Love SM. Inherited breast and ovarian cancer: What are the risks? What are the choices? JAMA 1993;269:1975.

quency of the 185delAG mutation in Ashkenazi Jews is approximately 1% and, with the 5382insC mutation, accounts for almost all *BRCA1* mutations in this population.[119,120] Analysis of germline mutations in Jewish and non-Jewish women with early-onset breast cancer indicates that approximately 20% of Jewish women who develop breast cancer before the age of 40 carry the 185delAG mutation.[121,122]

BRCA2

BRCA2 is located on chromosome 13q and spans a genomic region of about 70 kb of DNA. The 11.2-kb coding region contains 26 coding exons. It encodes a protein of 3,418 amino acids (Table 5.7). The *BRCA2* gene bears no homology to any previously described gene, and the protein contains no previously defined functional domains. The biologic function of *BRCA2* is not well defined, but, like *BRCA1*, it is postulated to play a role in DNA damage response pathways. *BRCA2* messenger RNA is also expressed at high levels in late G_1 and S phases of the cell cycle. The kinetics of *BRCA2* protein regulation in the cell cycle is similar to that of *BRCA1* protein, suggesting that these genes are coordinately regulated.[123]

The mutational spectrum of *BRCA2* is not as well established as that of *BRCA1*, but it is being defined at a rapid rate. To date, more than 250 mutations have been found.[124–134] Mutations are spread throughout the gene with no well-defined hot spots. All disease-associated mutations in *BRCA2* result in a truncated protein. As with *BRCA1* mutation carriers, the lifetime breast cancer risk for *BRCA2* mutation carriers is estimated to be in the range of 60% to 85%, and the lifetime ovarian cancer risk, while lower than for *BRCA1*, is still estimated to be in the range of 10% to 20%.[135,136] Breast cancer in *BRCA2* families appears as a classic mendelian trait of autosomal dominance with high penetrance. Approximately 50% of children of carriers inherit the trait. Unlike male carriers of *BRCA1* mutations, men with germline mutations in *BRCA2* have an estimated 6% lifetime breast cancer risk, representing a 100-fold increase over the male population risk (Table 5.7).

BRCA2-associated breast cancers are invasive ductal carcinomas, which are more likely to be well differentiated and express hormone receptors than *BRCA1*-associated breast cancer. *BRCA2*-associated breast cancer has a number of distinguishing clinical features, such as an early age of onset compared with sporadic cases, a higher prevalence of bilateral breast cancer, and the presence of associated tumors in some affected individuals, specifically ovarian, colon, prostate, pancreatic, gallbladder, bile duct, and stomach cancers, as well as malignant melanoma.[124,137]

A number of founder mutations have been also identified in *BRCA2*. The 6174delT mutation is found in Ashkenazi Jews with a prevalence of 1.2%.[138] Another *BRCA2* founder mutation, 999del5, has been observed in Icelandic and Finnish populations.[139,140] The Icelandic and Finnish mutation carriers share a common haplotype that covers a region spanning the *BRCA2* gene, suggesting that individuals who migrated from Finland to Iceland during ancient times carried this mutation.[141]

Gene Expression Profiles in BRCA1 and BRCA2 Breast Cancer

It has recently been shown that different groups of genes are expressed by breast cancers with *BRCA1* mutations when compared to those with *BRCA2* mutations.[142] RNA from specimens of invasive breast cancer taken from seven carriers of the *BRCA1* mutation, seven carriers of the *BRCA2* mutation, and seven patients with sporadic disease were compared using a microarray of 6,512 complementary DNA clones of 5,361 genes. Permutation analysis of multivariate classification functions established that the gene expression profiles of breast cancers with *BRCA1* mutations, breast cancers with *BRCA2* mutations, and sporadic breast cancers differed significantly from each other. An analysis of variance between the levels of gene expression and the genotype of the samples identified 176 genes that were differentially expressed in breast cancers with *BRCA1* mutations and those with *BRCA2* mutations.

Risk Management for BRCA1 and BRCA2 Carriers

Strategies for prevention of breast cancer in *BRCA1* and *BRCA2* carriers include: (1) prophylactic mastectomy and reconstruction, (2) prophylactic oophorectomy and HRT, (3) intensive surveillance for breast and ovarian cancer, and (4) chemoprevention (Tables 5.5 and 5.6). Although removal of as much breast tissue as possible will reduce the likelihood of *BRCA1* and *BRCA2* carriers developing breast cancer, mastectomy does not remove all breast tissue, and patients continue at risk because a germline mutation is present in any remaining breast tissue. The risk of ovarian cancer in *BRCA1* and *BRCA2* carriers is 10% to 40%, which is 10 times higher than that for the general population. Prophylactic oophorectomy is a reasonable prevention option in carriers, although it does not protect against the possibility of epithelial ovarian cancer arising spontaneously in the peritoneum. The American College of Obstetrics and Gynecology recommends that women with a documented *BRCA1* or *BRCA2* mutation consider prophylactic oophorectomy at the completion of childbearing or at the time of

menopause. Hormone replacement therapy should be discussed with the patient at the time of oophorectomy. For postmenopausal *BRCA1* and *BRCA2* carriers who have not had mastectomy, it may be advisable to avoid HRT as no data exists regarding the effect of HRT on the penetrance of breast cancer susceptibility genes.

Data regarding young women at high risk for breast cancer in the general population suggests that early detection and treatment are likely to be just as effective in *BRCA* mutation carriers as in noncarriers. A recent study indicated that breast cancers in *BRCA* mutation carriers have the same radiographic appearance as breast cancers in noncarriers. Therefore, screening mammogram is likely to be effective in *BRCA* mutation carriers, provided it is performed and interpreted with a high level of suspicion by an experienced mammographer. Present screening recommendations for *BRCA* mutation carriers who do not undergo prophylactic mastectomy include clinical breast exam every 6 months and mammography every 12 months beginning at age 25 because the risk of breast cancer in *BRCA* mutation carriers increases significantly after age 30. The Cancer Genetics Studies Consortium recommended yearly transvaginal ultrasound timed to avoid ovulation and yearly serum CA125 levels beginning at age 25 as the best screening modalities for ovarian carcinoma in *BRCA* mutation carriers who have opted to defer prophylactic oophorectomy. Despite the 49% reduction in the incidence of breast cancer in high-risk women taking tamoxifen in the NSABP Breast Cancer Prevention Trial, it is too early to recommend the use of tamoxifen uniformly for *BRCA* mutation carriers. Cancers arising in *BRCA1* carriers are usually high grade and are hormone receptor negative. A recent study showed that 66% of *BRCA1*-associated ductal carcinoma in situ is estrogen receptor negative, suggesting early acquisition of the hormone-independent genotype.

Other Susceptibility Alleles (reviewed in Martin and Weber[143])

p53 *and Li-Fraumeni Syndrome*

The first description of the Li-Fraumeni syndrome was in 1969, when four families with children with soft-tissue sarcomas were found to have an excess of sarcomas in other relatives. In addition, these families exhibited an excess of early-onset breast cancer and other cancers, such as childhood leukemia, adrenocortical carcinoma, and brain cancer (Table 5.9).[144] In 1990, the presence of germline *p53* mutations was described in approximately one half of families with LiFraumeni syndrome.[145] In women with germline *p53* mutations who survive childhood cancers, it is estimated that 50% will have developed breast cancer by age 50. Lifetime penetrance approaches 100%.[108]

STK11/LKB1 *and Peutz-Jeghers Syndrome*

Peutz-Jeghers syndrome is caused by germline mutations in *STK11/LKB1*, a serine threonine kinase located on chromosome 19q13.3.[146,147] Hamartomatous polyps in the small bowel and pigmented macules of the buccal mucosa, lips, fingers, and toes characterize Peutz-Jeghers syndrome. A retrospective study looking at cancer risk in Peutz-Jeghers families showed a risk ratio for breast cancer

Table 5.9 Incidence of cancer types in 24 Li-Fraumeni syndrome families.

	Age at diagnosis			
Cancer type	**0–14**	**15–44**	**>44**	**All ages**
Component cancers				
Breast carcinoma	0	49	11	60
Soft-tissue sarcoma	13	12	4	29
Brain tumors	12	15	1	28
Osteosarcoma	6	6	2	14
Leukemia	8	4	2	14
Adrenocortical carcinoma	5	0	0	5
Possible component cancers				
Lung carcinoma	0	7	12	19
Prostatic carcinoma	0	0	8	8
Pancreatic carcinoma	0	1	2	3
Melanoma	0	1	2	3
Other cancers	6	24	14	44
All cancers	50	119	62	231

Source: Adapted with permission from Garber JE, Goldstein AM, Kantor AF, et al. Follow-up study of twenty-four families with Li-Fraumeni syndrome. Cancer Res 1991;51:6094.

of 20.3:1 compared with control subjects.[148] The mean age of patients at the time of breast cancer diagnosis in this series was 39.

PTEN *and Cowden's Disease*

Cowden's disease is a rare autosomal dominant predisposition to both benign and malignant neoplasms. Breast cancer develops in 20% to 30% of carrier women. Other tumors seen among patients with Cowden's disease include adenomas and follicular cell carcinomas of the thyroid gland, polyps and adenocarcinomas of the gastrointestinal tract, and ovarian cysts and carcinoma.[149,150] Cowden's disease is caused by germline mutations in the *PTEN* gene (*MMAC1/TEP1*). *PTEN*, a tumor suppressor gene on 10q23.3, is a dual-specificity phosphatase.[151–154]

MSH2/MLH1 *and Muir-Torre Syndrome*

Muir-Torre syndrome is defined by the presence of sebaceous gland tumors and visceral malignancy. It is inherited in an autosomal dominant fashion with high penetrance.[133] Mutations in the same genes are associated with hereditary nonpolyposis colorectal cancer (HNPCC). The most common malignancy in Muir-Torre syndrome is colorectal cancer, seen in 50% of patients, but breast cancer occurs in approximately 25% of women carriers. The median age of patients at the time of a breast cancer diagnosis is 68.[155]

ATM *and Ataxia Telangiectasia*

Ataxia telangiectasia (AT) is a complex, autosomal-recessive disorder characterized by cerebellar ataxia, telangiectasia, immunodeficiencies, radiation sensitivity, and cancer predisposition, caused by homozygous mutations in the *ATM* gene. Epidemiological studies of AT families suggest that AT carriers (heterozygotes) may have an increased risk for developing breast cancer, although this observation is contro-

versial.[156–164] A number of studies have shown a risk ratio for breast cancer between 3.3:1 and 3.9:1 compared to control subjects.[161,163]

Low-Penetrance Breast Cancer Susceptibility Genes (reviewed in Martin and Weber[143])

Low-penetrance susceptibility alleles, sometimes called "modifier genes," are defined as polymorphic genes with specific alleles that are associated with an altered risk for disease susceptibility. Usually, the variants in these genes are common in the general population. Although each variant is associated with only a small increase in the risk for breast cancer in any individual, the attributable risk in the population as a whole is likely to be higher than for rare, high-penetrance susceptibility genes. Despite numerous studies published to date, the role of modifier genes in breast cancer susceptibility remains to be elucidated.

***P-450 Gene* CYP1A1**

CYP1A1 encodes aryl hydrocarbon hydroxylase, which is the primary catalyst in the conversion of estradiol to hydroxylated (catechol) estrogen.[165] As previously mentioned, a reduced estrogen exposure is protective for developing breast cancer, whereas increased estrogen exposure can increase the risk for developing breast cancer. Alterations in the activity of aryl hydrocarbon hydroxylase can lead to a change in the serum level of estrogen and thereby can affect breast cancer risk.

Glutathione* S-*Transferases

The glutathione *S*-transferases (GSTs) constitute a family of genes that encode for enzymes that catalyze the conjunction of reactive chemical intermediates to soluble glutathione conjugates to facilitate clearance. There are four classes of cytosolic GSTs, of which at least three are expressed in normal breast tissue.[166] The GSTμ genes have a null polymorphism that results in a total lack of enzyme in 50% of the population. Because the enzymes metabolize environmental carcinogens, there has been interest in determining whether homozygotes for the null alleles have an increased risk of breast cancer.[167] Recent findings suggest that the inability to metabolize carcinogens in this way does increase breast cancer risk.

N-Acetyltransferase

Polymorphisms in the *NAT2* gene are associated with an altered rate of metabolism of carcinogens. Wild-type alleles define a rapid acetylator phenotype, whereas homozygosity for any combination of three variant alleles results in a slow acetylator phenotype. Thus, having a slow phenotype could lead to altered metabolism of carcinogenic amines. The combination of smoking and slow acetylator status in *BRCA1* mutation carriers has been shown to result in an increased incidence of breast cancer in those individuals.[168] Altered steroid hormone metabolism could be the explanation for these findings.

Identifying Hereditary Risk for Breast Cancer

Identifying hereditary risk for breast cancer is a four-step process that includes: (1) obtaining a complete, multigeneration family history, (2)

assessing the appropriateness of genetic testing, (3) counseling the patient, and (4) interpreting the results of testing (Table 5.10).[169] Genetic testing should not be offered in isolation but only in conjunction with patient education and counseling. In many instances, referral to a genetic counselor is appropriate.

Initial considerations include determining whether the individual is an appropriate candidate for genetic testing and whether genetic testing will be informative for personal and clinical decision making. A thorough and accurate family history is essential to this process. It is essential to assess the father's side of the family as well as the mother's because one half of women with a *BRCA* mutation have inherited it from their fathers. To help clinicians advise patients about testing, statistically based models that determine the probability that an individual carries a *BRCA* mutation have been developed. The two original models, the Shattuck-Eidens[170] and Couch[171] models, were developed to predict the probability of a mutation in the *BRCA1* gene. In both models, the probability of harboring a *BRCA1* mutation is estimated from a woman's personal and family history of breast cancer, including age at diagnosis, the presence of unilateral or bilateral breast can-

Table 5.10 Breast cancer genetic susceptibility assessment.

Risk assessment

Increased risk for *BRCA* mutation

▼

Genetic counseling

Genetic basis of cancer susceptibility testing
Benefits, risks, and limitations of testing
Possible outcomes of testing
Limitations of methods
Psychological and social impact of testing
Alternatives to testing

▼

Patient accepts testing	**Patient declines testing**
Informed consent *BRCA* mutation analysis Explain test results Genetic counseling	*Plan surveillance*

▼

Deleterious mutation detected	**Indeterminate result**	**No deleterious mutation detected**
Plan intervention *Discuss testing of relatives*	Does mutation "track" with cancer? ◄ Yes No ►	*Plan surveillance*

Source: Adapted with permission from American College of Medical Genetics. Genetic Susceptibility to Breast and Ovarian Cancer; Assessment, Counseling and Testing Guidelines. Albany, NY: New York State Department of Health; 1999.

cer, and the presence of ovarian cancer. A subsequent model (Table 5.11) based on complete sequence analysis of both *BRCA1* and *BRCA2* in 238 high-risk women incorporated the likelihood of a mutation in either gene.[172]

A hereditary risk of breast cancer should be considered if a family includes two or more women with ovarian cancer or breast cancer before age 50.[172,173] Any woman diagnosed with breast cancer before age 50 or with ovarian cancer at any age should be asked about any first-, second-, and third-degree relatives on either side of the family with either of these diagnoses. Breast and ovarian cancer in the same individual, and male breast cancer at any age, also suggest the possibility of hereditary breast and ovarian cancer. The threshold for genetic testing should be lower in individuals who are members of ethnic groups in whom the mutation prevalence is known to be increased. For instance, the possibility of hereditary cancer should be considered for any Ashkenazi Jewish woman with early-onset breast cancer.[174,175]

Cumulative data reflecting observations from testing of thousands of women is now available to predict the probability of a *BRCA* mutation.[176] Mathematical models, such as the software BRCAPRO (www.jhsph.edu/biostats/brcapro.html), are also available to assess these gene mutation probabilities. BRCAPRO is a Bayesian computer program designed to estimate probabilities based on data entered by the physician. This model considers the structure of the family's pedigree, including both affected and unaffected family members, in estimating the probability of the presence of a mutation in *BRCA1* or *BRCA2*. Also included in the probability computation is data regarding age at breast and ovarian cancer diagnosis, presence of bilateral breast cancer, male breast cancer, and Ashkenazi heritage. The model is based on prevalence, penetrance, and mutation frequency data derived from persons who have had *BRCA* mutation analysis. The predictions from this model depend on the *BRCA* mutation penetrance estimates chosen. At present, studies to validate these models are underway.[177]

Table 5.11 Family history and *BRCA* mutation status.

First- or second-degree relative with				
Breast cancer at <50 y	**Ovarian cancer**	**Bilateral breast cancer or ovarian cancer**	**Breast cancer at <40 y**	**Chance of *BRCA* mutation (%)**
X				25
X			X	40
X		X		51
X	X		X	59
	X	X	X	71
X		X	X	79
X	X	X	X	89

Results are based on history taken from women diagnosed with cancer at <50 y.
Source: Adapted with permission from Frank TS, Manley, SA Olopade OI, et al. Sequence analysis of BRCA-1 and BRCA-2: Correlation of mutations with family history and ovarian cancer risk. J Clin Oncol 1998;16:2417.

BRCA Mutation Testing (reviewed in Evans et al.[177])

Only a healthcare provider can obtain genetic analysis for a *BRCA* mutation. Appropriate counseling for the individual being tested is strongly recommended, and documentation of informed consent is required (Table 5.10). The test that is clinically available for analyzing *BRCA* mutation is gene sequence analysis. In a family with a history suggestive of hereditary breast cancer and no previously tested member, the most informative strategy is to first test an affected family member. This person undergoes complete sequence analysis of both the *BRCA1* and *BRCA2* genes. If a mutation is identified, relatives are usually only tested for that specific mutation. An individual of Ashkenazi Jewish ancestry is usually tested initially for only the three specific mutations that account for most hereditary breast and ovarian cancers in that population. If that test is negative, it may then be appropriate to fully analyze the *BRCA1* and *BRCA2* genes.

Positive Test Result

A positive test is one that discloses the presence of a *BRCA* mutation, which prevents translation of the full-sized protein or is known to interfere in other ways with protein function. A woman who carries a mutation with such a deleterious effect has a lifetime breast cancer risk of 56% to 85%, as well as a greatly increased risk of ovarian cancer.[173]

Negative Test Result

A negative test result is interpreted according to an individual's personal and family history, especially with regard to whether a mutation has been previously identified in the family. If a specific mutation has been previously characterized in a patient's relative, the patient is in general tested only for that specific mutation. If the mutation is not present, the patient can be reassured that her risk of breast or ovarian cancer is no greater than that of the general population, regardless of family history, and the *BRCA* mutation cannot be passed on to the patient's children. In the absence of a previously identified mutation, a negative test result in an affected individual in general indicates that a *BRCA* mutation is not responsible for the familial cancer. However, it remains possible that there is an unusual abnormality in one of these genes that cannot yet be identified through clinical testing. It is also possible that the familial cancer is indeed due to an identifiable *BRCA* mutation, but that the individual who tested had sporadic cancer, a situation known as a "phenocopy." This is especially possible if the individual tested developed breast cancer close to the age of onset of the general population (over age 60) rather than before age 50, as is most characteristic of *BRCA* mutation carriers. Overall, the false-negative rate for *BRCA* mutation testing is in general held to be $\leq$5%.

Indeterminate Test Result

Some test results, especially where a single-base pair change (missense mutation) is identified, may be difficult to interpret. This is because single-base pair changes do not always result in a nonfunctional gene product. Thus, missense mutations not located within critical functional domains, or those that make only minimal changes in the sur-

rounding protein structure, may not be disease associated and are usually reported as indeterminate results. In communicating indeterminate results to patients, care must be taken to relay the uncertain cancer risk associated with this type of result and emphasize that ongoing research might clarify the meaning of such results. In addition, testing other family members to determine if that genetic variant "tracks" with their breast cancer can provide clarification of its significance. At present, indeterminate genetic variance accounts for approximately 12% of test results.

Informed Consent

Genetic testing for breast and ovarian cancer susceptibility is performed only with an individual's fully informed consent, including signing of a document to certify that informed consent was obtained. The review and signing of the informed consent form establishes that appropriate discussion with the patient has taken place but is not a substitute for the counseling process.

Patient Counseling

Unlike other diagnostic tests, the identification of hereditary susceptibility to breast cancer has significant implications not only for the individual being tested but also for the individual's relatives. A thorough discussion of the relevant issues should take place both before and after testing. Appropriate counseling includes discussion of the basic principles of hereditary cancer susceptibility, review of the patient's complete family cancer history, assessment of the woman's risk of cancer, and explanation of both how testing helps characterize the patient's risks and the implications of a positive, negative, or indeterminate result. Finally, implications for family members are discussed. Communicating genetic risk is challenging. Patients' understanding of their personal risk of cancer is often exaggerated, especially if they had a parent or sibling die of cancer at a young age, as they incorrectly assume that they have a 50% risk of cancer rather than a 50% risk of carrying the mutation. In addition, many people have difficulty appreciating probabilities. It is often helpful to describe risk in more than one way and compare it to the general population risk (e.g., "By age 50 your risk for breast cancer based on your family history alone is 7% or 1 in 14. If you test positive, your risk by age 50 would be between 33% and 50%, or at least 1 in 3. This is compared to a general population risk of 2%, or 1 in 50.")[177] Because genetic counseling can be time consuming and complex, one should consider referring patients to genetic counselors.

Health Insurance Issues

Concern has been expressed that the identification of hereditary risk for breast cancer can interfere with access to affordable health insurance. This concern refers to "discrimination directed against an individual or family based solely on an apparent or perceived genetic vari-

ation from 'normal' human genotype."[178] In a survey of approximately 300 genetic counselors in the United States, 85% stated that they would pursue genetic testing if they had a 50% risk of carrying a *BRCA* mutation, two thirds indicated they would not bill their insurance company for the tests, and some indicated they would use an alias.[179] To investigate this issue, Hall and colleagues conducted both in-person interviews with insurers and a direct market analysis, concluding that a person with a serious genetic condition who is presymptomatic faces little or no difficulty in obtaining health insurance.[180] This study found that there are few well-documented cases of health insurers inquiring about or utilizing presymptomatic genetic testing results in their underwriting decisions.[180]

The Health Insurance Portability and Accountability Act of 1996 (HIPPA) made it illegal in the United States for group health plans to consider genetic information a pre-existing condition or use it to deny or limit coverage. Most states have also passed laws that prevent genetic discrimination in the provision of health insurance. In addition, individuals applying for health insurance are not required to report whether relatives have undergone genetic testing for cancer risk, only whether those relatives have actually been diagnosed with cancer. At present, it appears that there is little or no documented evidence of genetic insurance discrimination resulting from available genetic tests.[179,180] This information should be conveyed to patients as part of their genetic counseling.

Translational Research

Prognostic and Predictive Biomarkers

Cancer biomarkers are of several types. Risk factor biomarkers are those associated with increased cancer risk. These include familial clustering and inherited germline abnormalities, proliferative breast disease with or without atypia, and mammographic densities. Exposure biomarkers are a subset of risk factors that include measurement of carcinogen exposure such as DNA adducts. Surrogate endpoint biomarkers (SEBs) are biologic alterations in tissue that occur between initiation and cancer development. These biomarkers are utilized as endpoints in short-term chemoprevention trials and include histological changes, proliferative markers, and genetic alterations leading to cancer (Table 5.12). Drug effect biomarkers (i.e., serum glutathione reductase activity, ornithine decarboxylase activity), which may or may not be directly related to carcinogenesis, are used to monitor the biochemical effect of drugs. Prognostic biomarkers provide information regarding cancer outcome irrespective of therapy, while predictive biomarkers provide information regarding response to therapy. Candidate prognostic and/or predictive biomarkers for breast cancer include indices of proliferation such as PCNA, BrUdR and Ki-67, apoptotic indicators such as bcl-2 and the bax/bcl-2 ratio, indices of angiogenesis such as VEGF and the angiogenesis index, growth factor receptors such as EGFr and *HER2/neu*, and *p53*.

Table 5.12 Surrogate endpoint biomarkers for breast cancer prevention.

Cohort	Primary endpoint	Cellular endpoints	Biochemical and molecular endpoints
Patients with atypical hyperplasia, lobular carcinoma in situ (LCIS), or ductal carcinoma in situ (DCIS)	Regression of atypical hyperplasia, LCIS, or DCIS	Mammographic density	Proliferation (PCNA, Ki-67)
		Histopathology	Apoptosis (bcl-2)
		Nuclear morphometry	Differentiation (sialyl Tn-antigen)
		DNA ploidy	Cell-regulatory molecules (EGFr, *HER2/neu)*
			Estrogen receptor
			IGF-I
			p53

***Proliferation Indices*[181–184]**

Proliferating cell nuclear antigen is a nuclear protein associated with a DNA polymerase whose expression increases in G_1, reaches its maximum at the G_1/S interface, and then decreases through G_2. Immunohistochemical staining for PCNA outlines the proliferating compartments in breast tissue. Good correlation is seen between PCNA and flow cytometrically determined cell cycle distributions based on DNA content. There is also good correlation between PCNA and BrUdR and the proliferation associated Ki-67 antigen. Individual proliferation markers are associated with slightly different phases of the cell cycle and are not equivalent. Proliferating cell nuclear antigen and Ki-67 expression are positively correlated with *p53* overexpression and with high S-phase, aneuploidy, high mitotic index, and high histological grade in human breast cancer specimens. They are negatively correlated with estrogen receptor content. The National Comprehensive Cancer Network currently recommends that S-phase fraction and Ki-67 expression be included in the initial workup of stage I, IIA, and IIB breast cancer. Patients with T1a or T1b cancers that overexpress Ki-67 and/or have a high S-phase fraction should be considered for adjuvant chemotherapy.

***Apoptosis*[185–187]**

Alterations in programmed cell death (apoptosis), which can be triggered by *p53*-dependent or -independent factors, may be important prognostic and/or predictive biomarkers in breast cancer. bcl2 family proteins appear to regulate a step in the evolutionarily conserved pathway for apoptosis, with some members functioning as inhibitors of apoptosis and others as promoters of apoptosis. bcl2 is the only known oncogene that acts by inhibiting apoptosis rather than directly increasing cellular proliferation. The death signal protein, bax, is induced by genotoxic stress and growth factor deprivation in the presence of wild-type *p53* and/or *APO1/fos*. The bax/bcl-2 ratio and the resulting formation of either bax-bax homodimers, which stimulate apoptosis,

or bax-bcl-2 heterodimers, which inhibit apoptosis, represent an intracellular regulatory mechanism with prognostic/predictive implications. In breast cancer, overexpression of bcl-2 and a decrease in the bax/bcl-2 ratio correlate with high histological grade, the presence of axillary lymph node metastases, and reduced disease-free and overall survival. Similarly, decreased bax expression correlates with axillary lymph node metastases, a poor response to chemotherapy, and decreased overall survival.

Angiogenesis[188–189]

Angiogenesis is necessary for the growth and invasiveness of breast cancer and promotes cancer progression through several different mechanisms, including delivery of oxygen and nutrients and the secretion of growth-promoting cytokines by endothelial cells. Vascular endothelial growth factor induces its effect by binding to transmembrane tyrosine kinase receptors. Overexpression of VEGF in invasive breast cancer has been correlated with increased microvessel density and recurrence in node-negative breast cancer. Recently an angiogenesis index has been developed in which microvessel density (CD31 expression) is combined with thrombospondin expression (a negative modulator of angiogenesis) and with *p53* expression. Both VEGF expression and the angiogenesis index may have prognostic and/or predictive significance.

Growth Factors/Receptors[190–192]

Overexpression of the epidermal growth factor receptor (EGFr) in breast cancer correlates with estrogen receptor negative status and *p53* overexpression. Similarly, using immunohistochemical techniques, increased membrane staining for the *HER2/neu* growth factor receptor in breast cancer has been associated with *p53* and Ki-67 overexpression and with estrogen receptor negative status. *HER2/neu* is a member of the EGFr family of growth factor receptors in which ligand binding results in receptor homodimerization and tyrosine phosphorylation by tyrosine kinase domains within the receptor. Tyrosine phosphorylation is followed by signal transduction, resulting in changes in cell behavior. An important property of this family of receptors is that ligand binding to one receptor type can also result in heterodimerization between two different receptor types that are coexpressed, resulting in transphosphorylation and transactivation of both receptors in the complex ("transmodulation"). In this context, the lack of a specific ligand for the *HER2/neu* receptor suggests that *HER2/neu* may function solely as a coreceptor, modulating signaling by other EGFr family members.

p53[193–197]

Wild-type *p53* plays a central role in cell cycle arrest, DNA repair, and programmed cell death. Mutation of the *p53* gene causes conformational changes in the *p53* protein and results in an increased protein half-life and overexpression in immunohistochemical assays. In breast cancer, *p53* overexpression correlates with high nuclear grade, high proliferative fraction, aneuploidy, *HER2/neu* overexpression, and hormone receptor negative status. Several retrospective studies of human

breast cancer suggest a role for *p53* in determining breast cancer prognosis and response to therapy.

Selection of the optimal multimodality therapy for breast cancer requires both an accurate assessment of prognosis and an accurate prediction of response to therapy. Unfortunately, current breast cancer biomarkers do not permit either of these. As a result, current multimodality therapy for breast cancer is empirical, based on the outcome of randomized clinical trials that examine average effects within populations. Clinicopathologic factors are used to separate breast cancer patients into broad prognostic groups, and treatment decisions are made on this basis (Table 5.13). With this approach, up to 70% of early breast cancer patients receive adjuvant chemotherapy that is either unnecessary or ineffective. As described above, a wide variety of biomarkers have been shown to individually predict prognosis and/or response to therapy, but when applied together with clinicopathologic factors, they do not improve the accuracy of either our assessment of prognosis or our prediction of response to therapy. As our knowledge regarding biomarkers for breast cancer increases, prognostic indices will be developed that combine the predictive power of several individual biomarkers with the relevant clinicopathologic factors. In laboratories at Brown University, molecular biomarkers (c-fos, c-myc, Haras, *p53*) were studied in a series of patients with stage I, IIA, and IIB breast cancer.[198] While single biomarker overexpression did not possess independent prognostic significance, the overexpression of three or more biomarkers identified breast cancers with an aggressive phenotype, accurately predicting adverse disease-free and overall survival (Table 5.14). At the University of Alabama at Birmingham, we recently completed an analysis of molecular biomarkers of breast cancer prognosis using breast tissues from women accrued prospectively to the Alabama Breast Cancer Project (1975 to 1978).[199] Criteria for entrance into the Alabama Breast Cancer Project were T1–3 breast cancer with M0 status. Age, nodal status, and histological grade were also documented. Patients were randomized to radical vs modified radical mastectomy. Node-positive patients were also randomized to adjuvant cyclophosphamide, methotrexate, and 5-flourouracil (CMF) vs melphalan. Using immunohistochemistry, archival breast cancer tissues were studied for *HER2/neu*, transforming growth factor-α (TGF-α), *p53*, cathepsin D, bcl-2, and hormone receptor status.

Table 5.13 Traditional prognostic and predictive factors for breast cancer.

Tumor factors	Host factors
Nodal status	Age
Tumor size	Menopausal status
Cytological/nuclear grade	Family history
Lymphatical/vascular invasion	Previous breast cancer
Pathologic stage	Immunosuppression
Hormone receptor status	Nutrition
DNA content (ploidy, S-phase)	Prior chemotherapy
Extensive intraductal component	Prior radiotherapy

Table 5.14 Overall survival in breast cancer by prognostic factor.

Variable	Univariate analysis	Multivariate analysis
Age	0.079*	0.004*
Altered gene expression†	0.035	0.008
Lymphadenopathy	0.244	0.051
Tumor size	0.130	0.109

*P value.
†c-fos, c-myc, Ha-ras, p53.

Three hundred and eleven patients were accrued to the Alabama Breast Cancer Project. Paraffin-embedded breast cancer tissues for 90 patients were available for immunohistochemical analysis of molecular biomarkers. Univariate analysis showed nodal status, *HER2/neu* expression, and *p53* expression to have prognostic significance (Table 5.15). Coexpression of *HER2/neu* and *p53* was also found to have prognostic significance by log rank test (Table 5.16). Coexpression of *HER2/neu* and *p53* has been reported in several studies, with the frequency of coexpression being as high as 42%.[200–215] Patients whose breast cancer tissues coexpress *HER2/neu* and *p53* have been found to have a poor prognosis in several studies.[200,203,205,206,210,211,213,215] It has been postulated that breast cancers coexpressing *HER2/neu* and *p53* (both genes map to chromosome 17) have lost a key mechanism for control of cell proliferation and gained an activator of malignant cell potential, resulting in a highly malignant tumor phenotype.[202,216] However, some studies have shown *HER2/neu* and *p53* coexpression to have no impact on prognosis, while some have shown a better prognosis for breast cancers coexpressing *HER2/neu* and *p53*.[204,207,209] These differences may reflect the effect of varying therapeutic regimes on the interaction between *HER2/neu* and *p53*.[216] Breast cancer patients whose

Table 5.15 Disease-specific survival in breast cancer by prognostic factor.

Prognostic factor	No. of patients	Log rank test (univariate analysis)	Rank regression procedure (multivariate analysis)	Median survival time (y)
T-stage				
T1–T2	67	$P = 0.066$ (vs T1–T2)	$P = 0.012$ (vs. T1–T2)	>21
T3	17			5
Nodal status				
Negative	39			>21
1–3 positive	27	$P = 0.028$ (vs negative)	$P < 0.001$	16
>4 positive	23	$P < 0.001$ (vs negative)	(negative vs 1–3 vs >4)	3
HER2/neu				
Negative (0)	58			>21
Positive (1–3)	28	$P = 0.003$ (vs negative)	$P = 0.012$ (vs negative)	4
p53				
0–1	50			<21
2–6	26			>21
7–8	13	$P < 0.001$ (vs 0–1, 2–6)	$P = 0.011$ (vs 0–6)	2

Table 5.16 Prognostic significance of *HER2/neu* and p53 coexpression

Coexpression of			No. of patients	Log rank test (univariate analysis)
HER-2/neu	+	p53		
Negative (0)*	+	Low (0–6)	51	
Positive (1–3)	+	Low (0–6)	22	$P = 0.011$ (vs 1)
Negative (0)	+	High (7–8)	7	$P = 0.0002$ (vs 1)
Positive (1–3)	+	High (7–8)	6	$P = 0.0001$ (vs 1) $P = 0.0009$ (vs 2)

*Immunostaining score.

tumors coexpress *HER2/neu* and *p53* have an improved 10-year survival rate when treated with high-dose fluorouracil, adriamycin, and cyclophosphamide (FAC).[214]

The extensive data already accumulated concerning prognostic and predictive biomarkers for breast cancer makes exhaustive analysis of all relevant molecular abnormalities a daunting task. However, the technologies necessary for such a task are being developed and are being tested in human cancer tissues. Microdissection techniques combined with high-density oligonucleotide arrays and other high-throughput analyses of gene expression now enable us to study breast cancer tissues for multiple alterations simultaneously. As bioinformatics provides us with the tools to categorize and analyze the immense amount of data being generated, these technologies will allow us to develop a detailed stratification of breast cancer patients for the purpose of accurately assessing prognosis and predicting response to therapy.

Biomarkers for Breast Cancer Prevention

A serious rate-limiting factor in the development of new chemopreventive agents for breast cancer is the lack of a validated model for phase II clinical testing. A satisfactory model should: (1) provide for reliable and reproducible sampling of precancerous tissue that contains the SEBs of interest, (2) accomplish the sampling with a minimum of subject discomfort, (3) require no out-of-pocket expense for the subject, and (4) utilize only validated SEBs.[217] At present, several models are being utilized for Phase II testing of agents: (1) a short-term ductal carcinoma in situ (DCIS) model in which women with incompletely resected DCIS are randomized to receive drug or placebo for a 2-week interval between core biopsy and the definitive surgical procedure; (2) an intermediate or long-term fine-needle aspiration (FNA) model in which high risk women without cancer but with cytological evidence of hyperplasia with atypia or evidence of abnormal molecular markers (EGFr, *p53*, DNA aneuploidy) are treated with drug or placebo for 6 months and then are reaspirated; and (3) a core biopsy model in which women who undergo core biopsy of a palpable or mammographically defined area and are found to have atypia are randomized to drug or placebo and then rebiopsied following treatment. An addi-

tional model being tested is the use of nipple aspirate fluid (NAF) from high-risk women in which cytological characteristics or a variety of biochemical markers can be monitored.[218,219]

Random periareolar FNA is well tolerated, and FNA cytology in combination with Gail risk assessments has been demonstrated in a prospective study to identify women at very high short-term risk for breast cancer.[220] In a study of 480 high-risk women, hyperplasia with atypia observed in random FNA aspirates was associated with an observed breast cancer incidence of 3% per year over the ensuing 4 years, irrespective of Gail model risk assessment. Women with hyperplasia without atypia, but a 10-year breast cancer risk of 4% or higher by Gail model risk assessment, had an observed breast cancer incidence of 1% per year over the subsequent 4 years of follow-up. In comparison, there is a little experience with ductal lavage as a method of obtaining sequential tissue biopsy specimens. The reproducibility of repeated lavages and cytological characterization over a 6-month interval is unknown. Ductal lavage is in general performed on those ducts that yield NAF after manual massage. Results reported to date from a consortium study indicate that 90% of pre- and perimenopausal high-risk women will yield NAF and that 80% of women producing NAF will successfully undergo a lavage in which 10 or more ductal cells are obtained.[221] The median number of cells from a successful lavage is reported to be 13,000 when 3 ducts are cannulated. Young women with spontaneous nipple discharge or who have previously breastfed are more likely to have a successful lavage. Cell numbers are in general higher in pre- or postmenopausal women receiving HRT when compared to the number of cells obtained from postmenopausal women not on HRT.

Selection of SEBs to determine response to phase II agents is controversial.[222] At present, there are no validated SEBs for breast chemoprevention trials. Morphology and proliferation biomarkers are the most frequently utilized. Morphological changes of DCIS, lobular carcinoma in situ (LCIS), atypical intraductal hyperplasia, and hyperplasia without atypia are clearly associated with an increased short-term risk of breast cancer (0.36%/y for hyperplasia up to 2.5%/y for DCIS in the first 10 to 15 years after diagnosis).[223–228] Ductal carcinoma in situ is often focal and requires a treatment intervention, which limits its utility as a response biomarker. Further, it is not clear how reversible DCIS is following short-term treatment with a minimally toxic chemoprevention agent. On the other hand, LCIS and hyperplasia with or without atypia do not require a treatment intervention and are often diffusely distributed, which suggests that they can be utilized as response biomarkers in intermediate and long-term chemoprevention trials. [223,225,226,229–231]

Other tissue-based biomarker abnormalities, which are potentially reversible and are currently being explored in phase II trials, have already been presented in this chapter and include elevated proliferation indices such as Ki-67 and PCNA[181–184]; ER overexpression[232,233]; markers of oncogene overexpression such as *Her2/neu* and EGFr[190–192]; altered levels of insulin-like growth factor receptor (IGFR), IGF-1, and

IGF binding protein-3 (IGFBP-3)[234–239]; indicators of apoptotic imbalance including an increased bcl-2/bax ratio[185–187]; markers of disordered cell signaling such as *p53* protein accumulation or nuclear exclusion[193–197]; altered levels of p16, p21, p27, cyclin D_1, and cyclin E[240–248]; alteration of differentiation signals such as c-myc and related proteins[249–251]; loss of differentiation markers such as TGF-β-II receptor and retinoic acid receptor[252–254]; cell adhesion alteration such as CD44 isoform expression and E-cadherin loss[255,256]; alteration of angiogenesis proteins such as VEGF overexpression[188,189]; and thrombospondin I loss[257–260]; and methylation abnormalities.[256,261] None of these have been validated as SEBs, although alterations in all of these biomarkers have been associated with precancerous lesions.[190–192,197,245,256,262–269] Expression of many of these markers is known to vary with fixation technique and with the antibody used for detection, as well as with the antigen retrieval methods used.[270] Further, biomarker expression may vary with the phases of the menstrual cycle, with menopause status, and with age.[239,271–276] Serum biomarkers have particular appeal because they do not require repeated breast tissue biopsies. Insulin-like growth factor is a potent epithelial mitogen that can synergize with estrogen to stimulate growth of human breast cancer cells and prevent apoptosis even in the presence of chemotherapy agents.[238] A decrease in IGFBP-3 and increased levels of IGF-1 have been noted during transformation of preneoplastic breast epithelial cell lines.[237] Premenopausal women with breast cancer have increased IGF-1 to IGFBP-3 ratios when compared to controls.[277] Further, an increase in IGF-1 levels in young women who have at least one relative with breast cancer has been observed.[278] A decrease in IGF-1 was noted in premenopausal women during treatment with fenretinide (4-HPR) in a phase III trial. There was a concomitant decrease in breast cancer incidence.[279–281]

Molecular-Based Therapy

HER2/neu[282,283]

The first evidence of the clinical importance of *HER2/neu* overexpression in breast cancer came from a report of *HER2/neu* gene amplification in poor prognosis breast cancer. Since then, repeated studies have produced conflicting results, but in node-positive patients the initial results have been confirmed. In addition, examination of the extent of *HER2/neu* activation (phosphorylated vs unphosphorylated) can separate patients into those with a poor vs those with a better prognosis. The National Comprehensive Cancer Network (NCCN) recommends that evaluation of *HER2/neu* expression be a part of the standard workup of patients with breast cancer, but at present it is unclear how precisely to utilize that information. In individual patients for whom the best choice of adjuvant therapy is not clear, *HER2/neu* overexpression may lead to a more aggressive option despite the absence of prospective trials. In choosing an adjuvant chemotherapy regimen, evidence suggests that a doxorubicin-containing regimen is preferred for patients with *HER2/neu* overexpressing cancers. The gene for topoiso-

merase IIα, an enzyme believed to be an important intracellular target for doxorubicin, lies in the *HER2/neu* amplicon and may be coamplified with *HER2/neu*.

The high level of expression of *HER2/neu* in some breast cancers has made it a therapeutic target. One of the first therapeutic strategies studied was inhibition of *HER2/neu* expression by anti-*HER2/neu* antibodies. The Herceptin monoclonal antibody was initially produced as a murine antibody and then was modified for human use. Results from a large phase III study of patients with metastatic breast cancer, who were randomized to chemotherapy with or without Herceptin, showed a doubling of the response rate and a significant prolongation of the time to disease progression for patients receiving Herceptin. These and other similar results led the FDA to approve Herceptin as a therapy for patients with *HER2/neu*-overexpressing metastatic breast cancer, either as first-line treatment in combination with paclitaxel or as a second- or third-line single therapy. Another strategy advancing through clinical development is the use of adenoviral *E1A* delivery to suppress *HER2/neu* gene transcription. Transduction of the *E1A* gene has been shown to interact with the *HER2/neu* promoter, resulting in transcriptional downregulation. This gene therapy strategy has shown promising results in murine breast cancer models and in human phase I studies. Both anti-*HER2/neu* antibodies and adenoviral E1A delivery exemplify the potential of translational research, which involves a progression from basic molecular biology to an understanding of cell biology, to discovery of prognostic and predictive biomarkers in human cancer, and finally to molecularly based, targeted therapy.

***Angiogenesis*[284]**

Angiogenesis, the formation of capillaries from established blood vessels, is an essential requirement for cancer growth. Once cancers gain the ability to induce angiogenesis in surrounding tissues ("angiogenesis switch"), they are able to proliferate rapidly and metastasize. Increased understanding of the biology of angiogenesis has led to the development of new classes of drugs (Table 5.17) that are now being tested in human trials. Once the angiogenesis switch is thrown, cancer cells begin to secrete high levels of molecules, such as VEGF, that stimulate the proliferation of adjacent endothelial cells and are potential targets for antiangiogenic drugs. The molecular basis of the angiogenic switch appears to be an accumulation of activated oncogenes that induce the transcription of angiogenic growth factors. Endothelial cells

Table 5.17 Antiangiogenic drugs in clinical development.

Class of drug	Mode of action
MMP inhibitors	Inhibit MMP-2 and MMP-9
VEGF receptor inhibitors	Inhibit binding of VEGF to receptor
Anti-VEGF antibody	Blocks the VEGF receptor
Anti-integrin antibodies	Cause endothelial apoptosis
Vascular targeting agents	Fixes complement and causes vasculitis

respond to angiogenic factors such as VEGF via transmembrane receptors (VEGF receptor). Specific inhibitors of these receptors have been developed, such as SU5416. Phase I human trials of SU5416 have been completed. Anti-VEGF antibodies have also been developed to block the VEGF receptor. Phase I human studies of anti-VEGF antibody have also been completed.

After exposure to growth factors, endothelial cells express high levels of the extracellular matrix protein receptor $\alpha\nu\beta3$ integrin. In animal models, administration of antibodies to $\alpha\nu\beta3$ integrin causes apoptotic cell death of endothelial cells in new blood vessels, making it a potential therapeutic agent. Phase I human studies of anti-integrin antibodies have been completed. For new capillaries to develop, cancer cells also need to degrade the proteins of the extracellular matrix. This is accomplished by the release of a family of enzymes called matrix metalloproteases (MMPs). Two members of the MMP family known to be involved in breast cancer angiogenesis are MMP-2 and MMP-9, which degrade collagens present in basement membranes. Matrix metalloprotease inhibitors have been developed to block angiogenesis, to inhibit cancer growth, and inhibit the ability of cancer cells to metastasize by invading blood vessels. Randomized phase II human studies of such inhibitors have been completed. An alternative strategy is the use of drugs, such as CM101, which are selectively toxic toward endothelial cells in new blood vessels through activation of complement. The result is a severe vasculitis in new blood vessels, which leads to tumor necrosis. Phase I human studies of CM101 have been completed. In general, the low toxicity of anti-angiogenic drugs makes them attractive agents to integrate with adjuvant treatment protocols.

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6

Polyposis Syndromes

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Genetics

Polyposis syndromes are rare entities identified by the presence of multiple polypoid lesions of the gastrointestinal (GI) tract. These syndromes are usually inherited in an autosomal dominant manner but may result from spontaneous mutations. The polyps may be nonneoplastic such as Peutz-Jehgers syndrome (PJS) and juvenile polyposis, or more commonly, the polyps are neoplastic and related to abnormalities of the adenomatous polyposis coli gene (*APC*). These mutations can result in familial adenomatous polyposis (FAP), attenuated adenomatous polyposis coli (AAPC), or Gardner's or Turcot syndrome.

The *APC* gene has been localized to chromosome 5q21,[1,2] and its role in the pathogenesis of the neoplastic polyposis syndromes confirmed.[3–6] The *APC* gene is a tumor suppressor gene that is involved with apoptosis or programmed cell death,[7,8] with inactivation resulting in initiation of tumorigenesis through disruption of cell number homeostasis.[9–11] Mutations in the *APC* gene can result from substitution of a single base in the DNA strand. This substitution can change a single amino acid, a missense mutation, with functional consequences depending on the position and the new amino acid substituted. More commonly, the base substitution may signal for the termination of translation, a stop codon. These nonsense mutations result in a truncated protein. Segments of the *APC* gene can also be deleted, resulting in an absence of a segment of the final protein. If the number of bases deleted is not a multiple of three, this results in a frame shift mutation and usually premature termination of translation of the DNA and a truncated protein.

Two normal *APC* protein molecules are linked together (homeodimers) to produce a biologically active protein. Truncated *APC* proteins can bind to normal *APC* proteins to form an inactive homeodimer.[12] This binding is dependent on the length of the abnormal protein, with the truncated protein resulting from a proximal mutation unable to effectively bind with a normal molecule resulting in mild manifestations (AAPC), while the longer length proteins produced from

more distal mutations will bind and inactivate a normal *APC* protein and result in aggressive forms of the disease.[13,14]

While attempts to utilize genotypic information to predict phenotypic expression of the disease have not been completely successful, certain specific patterns as shown in Figure 6.1 can be identified. The retinal abnormality associated with FAP, congenital hypertrophy of the retinal pigmented epithelium (CHRPE), is correlated with truncating mutations located between codons 463 and 1,444.[15–17] The attenuated form of the disease, AAPC, is characteristic of truncating mutations before codon 157 or after codon 1,464,[13,18] while an aggressive form of the disease with large numbers of polyps is related to mutations between codons 1,250 and 1,464.[14,19,20] Desmoid tumors and osteomas are associated with abnormalities between codons 1,403 and 1,578.[21,22]

Certain abnormalities are associated with specific ethnic groups. An example of this is the I1307K missense mutation in the *APC* gene, which can lead to familial colorectal cancer in Ashkenazi Jews. This alteration involves the change of a single base from thymidine to adenine in codon 1,307 and is present in about 6% of Ashkenazi Jews. It is not associated with polyposis, but does appear to confer a twofold increased risk of colorectal cancer.[23–25]

Although genotypic characteristics can be used to predict clinical manifestations with some accuracy, there are reports of identical *APC* mutations resulting in FAP in one family and Gardner's syndrome in another.[26,27] It has also been reported that identical *APC* mutations have resulted in severe manifestations in one family and mild disease in another.[28] These differences may be the result of modifying genes or environmental factors. One possible modifying gene identified in mice with multiple intestinal neoplasia (MIN mice) is a gene that codes for a secreted phospholipase.[29,30] The finding that nonsteroidal antiinflammatory drugs (NSAIDs) can lead to prevention and regression of polyps[31,32] through cyclo-oxygenase inhibition in the arachidonic acid metabolic pathway suggests that environmental factors can also alter the phenotypic expression.

The nonneoplastic polyposis syndromes are rare and less extensively studied. A defect of the serine threonine kinase gene, *STKII*, located on chromosome 19p13.3 is believed to be the etiology of PJS.[33] The etiology of juvenile polyposis was thought to be a defect in a protein tyrosine phosphatase gene, *PTEN*, located on chromosome 10q 23, but now it appears more likely that a truncating mutation in the Smad4 gene on chromosome 18q 21.1 is the etiology.[34–36]

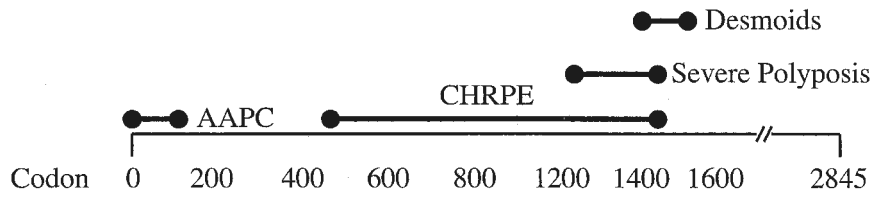

Figure 6.1 Genotype–phenotype correlations: The usual phenotypic expression of abnormalities in specific regions of the *APC* gene.

Familial Adenomatous Polyposis

Clinicopathologic Features

A familial syndrome characterized by the presence of colonic polyposis was recognized and reported by Cripps in 1882.[37] The malignant potential of these polyps was suggested by Handford in 1890[38] and confirmed in 1925 by Lockhart-Mummery.[39] Usually the disease is inherited in an autosomal dominant pattern, but as many as 30% of patients appear to develop the disease from a spontaneous mutation of the *APC* gene.[40,41] Affected individuals have a near 100% lifetime risk of developing colorectal cancer.[42,43]

The syndrome of FAP is distinguished by the presence of greater than 100 colonic adenomatous polyps. The number of polyps present can differ between affected members of the same family. The polyps can also vary in size, shape, and distribution, but are usually small, with less than 1% exceeding 1 cm, and sessile. Although all areas of the colon are involved in the fully developed syndrome, there appears to be a predilection for the rectum and left colon with a greater number of polyps and an earlier age of onset. Histologically tubular adenomas predominate, but tubulovillous and villous adenomas become more common with advanced disease. The polyps are initially benign but undergo the polyp to carcinoma sequence over several years. Polyps will be present in 75% of affected individuals before age 20, and colorectal cancer develops at an average age of 39. Multiple carcinomas are present in half of these patients. The prognosis after development of colorectal cancer is the same as that for the nonpolyposis patients with colorectal cancer and is related to the stage of the disease at the time of treatment. In addition, there are frequently extracolonic manifestations of *APC* gene abnormalities (Table 6.1).

Table 6–1 Extracolonic manifestations of FAP.

Duodenal adenomas	80–90%	12% lifetime cancer risk
Gastric fundic gland hamartomas	50–70%	Must be distinguished from the much less common gastric adenoma
Hepatoblastoma	1%	Develops during early childhood
Desmoid tumors	12–38%	Surgery for desmoid-related complication will be required in 27%
Osteomas	80%	Rarely results in cosmetic problems
Congenital hypertrophy of the retinal pigment epithelium	80%	Useful as a marker for screening purposes

Extracolonic Manifestations

Gastroduodenal Polyps

Duodenal adenomatous polyps will develop in 80% to 90% of patients with FAP.[44–46] There is a serious risk of malignant change in these lesions, with the estimated risk of periampullary cancer in FAP patients being increased to 100 times that of the nonpolyposis population.[44,47,48] The risk of duodenal or periampullary cancer appear to be approximately 12%,[47] with an average interval of 16 years between diagnosis of FAP and the upper GI malignancy.[48] Adenomas can also occur in the jejunum and ileum. The incidence of these lesions is 40% and 10%, respectively.[49] The malignant potential of these lesions is unknown.

While gastric polypoid lesions are a common feature of FAP, there appear to be regional differences in the histological types of polyps. The incidence of gastric adenomas is 36% in a study of Japanese patients[50] and 9% in two studies of non-Japanese patients.[45,51] The risk of gastric adenocarcinoma in patients with FAP compared to the nonpolyposis population has been variously reported to be increased by seven-fold in a study of Korean patients,[52] three-fold increased in Japanese patients,[53] and not increased in a US study.[54]

Another type of gastric polyp, the fundic gland polyp, is present in the majority of patients with FAP worldwide.[51,55] Pathologically, these lesions are multiple sessile lesions located in the gastric fundus. Microscopically, they are composed of dilated, cystic fundic glands and are considered to be hamartomas with no malignant potential.

Desmoid Tumors

Desmoid tumors consist of masses of fibroaponeurotic tissue. While such tumors are rare, patients with FAP have a 1,000-fold greater risk of developing desmoids compared to the general population.[56] The incidence in polyposis patients is 12% to 38%[42,57–60] with a peak age at 28–31. Familial clustering of desmoid tumors in FAP patients has been noted.[56,61,62]

Although desmoid tumors have been associated with *APC* abnormalities in many different locations, an increased risk has been associated with mutations located between codons 1,403 and 1,578 in the *APC* gene.[21,58] In one study, 36 of 39 patients with an *APC* mutation in codon 1,444 developed desmoids.[22] Trauma and hormones may also be involved in the etiology of desmoid tumors. There is evidence to suggest a relationship between desmoids and estrogen with an increased incidence in women of reproductive age and during pregnancy.[63,64] Regression of these tumors has also been reported after decreasing estrogen by physiological, pharmacological, or surgical means.[65,66] Decreasing the inflammatory response with the NSAID sulindac may also help control desmoids.[44]

Desmoid tumors associated with FAP usually present within 2 to 3 years after an abdominal surgical procedure and are located intra-abdominally in 80% of patients, in the abdominal wall in 18%, and extra-abdominally in 2%.[42,67] Multiple sites are affected in 5% to 38% of patients.[56,64] Histologically, the tumors are composed of benign appearing fibroaponeurotic tissue with mature differentiated fibroblasts

Table 6.2. Natural history of desmoid tumors.

Regress spontaneously	10%
Cyclical growth/regression	30%
Stable or slow growth	50%
Aggressive growth	10%

in an abundant collagen matrix. Abdominal wall desmoids tend to be encapsulated while intra-abdominal desmoids are more commonly dense fibromatosis without distinct margins. Intra-abdominal desmoids are usually located in the small bowel mesentery, where they are intimately associated with the small bowel vessels.[68,69] In contrast to sporadic desmoid tumors, which tend to be slow growing and indolent, those associated with FAP are much more variable. It has been reported that 10% will regress completely, 29% will undergo cycles of growth and resolution, 47% will remain stable after diagnosis, and 10% will grow rapidly (Table 6.2).[42]

Desmoids usually grow to a considerable size before causing symptoms. Pain is the predominant symptom in about one half of patients. Intra-abdominal desmoids can cause compression and obstruction of the small intestine. The mesenteric blood vessels may become occluded and result in ischemia with sepsis,[70] while retroperitoneal desmoids can lead to compression of the ureters with hydronephrosis. Surgery for a desmoid-related problem will be required in 27% of patients with an intra-abdominal desmoid.[71]

Congenital Hypertrophy of Retinal Pigmented Epithelium

Congenital hypertrophy of the retinal pigment epithelium is present in 87% to 95% of patients with FAP.[72,73] It rarely occurs with *APC* mutations before codon 400 or after codon 1,444 but is almost universal with abnormalities between codons 468 and 1,387.[15,22] The ocular findings are consistent between affected members of the same FAP family.[53] While the finding is of no functional significance, it has been used as a marker for screening purposes.[74,75]

Osteoma

The classic location of osteomas is the mandible and maxilla although localized thickening of the cortex of the long bones is not uncommon. These lesions have been reported to be present over 90% of patients with FAP when tomography of the maxilla and mandible has been obtained. Most are 3 to 10 mm and have an increased radiologic density.[76] These bony tumors may predate the onset of intestinal manifestations of FAP by many years. In the past, radiological examination of the mandible and maxilla was suggested as a screening method for patients at risk for FAP,[77] but newer methods have made this unnecessary.

Thyroid Malignancy

Women with polyposis have a reported 1% to 2% incidence of thyroid carcinoma, which is a 40- to 50-fold increased risk compared to the nonpolyposis population. The cancers are usually papillary and de-

tected before the onset of intestinal manifestations.[78] There does not appear to be an increased risk of thyroid malignancies for males affected with FAP.

Hepatobiliary Tumors
There appears to be a markedly increased incidence of hepatoblastoma in patients with FAP. These tumors usually develop during childhood, prior to the onset of intestinal polyps, and are associated with an elevated α-fetoprotein.[79–81] There also appears to be an increased risk of hepatocellular carcinoma, but this is less common.[82] The risk of bile duct carcinomas also seems to be significantly increased, but these tumors are still rare.

Dental Findings
Classic descriptions of the Gardner's syndrome variant of FAP have included an association with dentigerous cysts and supernumerary teeth,[83] but the incidence of these problems does not seem to be increased over the non-polyposis population.[76]

Central Nervous System Tumors
Malignant tumors of the central nervous system (CNS) are a feature of the Turcot's variant of FAP and are included in the discussion of that syndrome.

Dermatologic Lesions
Epidermoid inclusion cysts are common in the polyposis and non-polyposis populations. Patients affected with FAP can develop these lesions before puberty, which is rare in the unaffected population and can alert the clinician to the potential for intestinal polyposis. These cysts are most commonly located on the head, neck, and arms.

Clinical Variants

Attenuated FAP
Attenuated FAP is characterized by a reduced number of polyps and a delayed onset of the manifestations of the disease (Table 6.3). While patients with FAP have over 100 polyps, the average with AAPC is 30. The polyps are more likely to be right colonic and develop after 25 years of age,[18] in contrast to FAP, where there is a predilection for the rectum and left colon, and the polyps develop before age 25. Colorectal cancer occurs at an average age of 39 years in FAP and 51 years in AAPC.[20,43] The extracolonic manifestations associated with clinical AAPC are the same as those with FAP.[27] Genetically, AAPC is associ-

Table 6.3 Comparison of AAPC and FAP.

AAPC	FAP
Onset age 20–30	Onset before age 18
Right colon polyps most common	Predilection for rectum and left colon
Fewer polyps (30 polyps average)	Over 100 polyps
Risks of colorectal cancer over 90%	Risk of colorectal cancer over 90%
Average age at cancer: 59	Average age at cancer: 39

ated with, but not limited to, truncating mutations of the *APC* gene before codon 157 or after codon 1,464.[13,18]

Gardner's Syndrome

Originally, Gardner's syndrome was described as polyposis with associated osteomata, cutaneous cysts, and fibromata.[84] Later, the fibromata were deemed to be desmoid tumors. The extracolonic manifestations are the prominent feature of the Gardner's syndrome variant but can also be seen in FAP. Desmoid tumors and CHRPE in particular may occur in persons thought to have FAP.[26] There is no specific *APC* mutation that correlates with Gardner's syndrome; however, desmoid tumors are associated with mutations between codons 1,403 and 1,578.[21,22]

Turcot Syndrome

The association of malignant tumors of the CNS and polyposis was described by Turcot in 1959.[85] Most families with the clinical diagnosis of Turcot syndrome have mutations of the *APC* gene, but there is no specific defect that correlates with the syndrome. Medulloblastoma-type tumors seem to predominate, although there are reports of anaplastic astrocytomas and ependynomas. In Turcot syndrome, the CNS manifestations may precede the polyposis.

Diagnosis and Evaluation

Most patients with polyposis are asymptomatic until the development of colorectal carcinoma. The diagnosis is usually made during the evaluation of a patient with a family medical history suggestive of an inherited colorectal cancer syndrome (Table 6.4). The possibility of a dominantly inherited colorectal cancer syndrome is more likely as the number of affected individuals and generations increases and the age at diagnosis of the affected individuals decreases. The family medical history can also provide valuable information regarding the natural history and manifestations of the problem in the family. While not perfect, predictions about the age of onset and severity of the disease can be discerned, as well as the risk of extracolonic manifestations. The distinction between AAPC, Gardner's, and Turcot's variants is determined by the family medical history and clinical findings more so than by genetic testing. Despite the importance of the family medical history, it is often omitted[86,87] or inaccurate.[88,89]

The family history will show no evidence to suggest a hereditary cancer syndrome in 20% to 30% of patients with FAP. Reasons for this include new mutations, adoption, questions of paternity, or denial.[40,41] In this instance, the diagnosis is usually made after the on-

Table 6.4 Indications for gene testing.

100 or more colorectal adenomas
First-degree relatives of patients with FAP
20 or more cumulative colorectal adenomas
First-degree relatives of patients with attenuated FAP
Presence of extracolonic manifestation

set of symptoms related to extracolonic manifestations or colorectal cancer.

Management of FAP

Genetic Counseling

The diagnosis of an inherited cancer syndrome, whether made on the basis of the family medical history, clinical findings, or genetic testing results, is a calamitous event with ramifications for patients and their families. Management options include aggressive screening regimes, chemopreventive agents, and prophylatic surgery. Regardless of the modalities chosen, a lifetime of surveillance is needed. Optimal results require patients to comply fully with their treatment plans. This compliance is enhanced when the patient is fully informed and participates in the decision-making process. Through genetic counseling, a patient can be educated about the nature of his or her disease, the possible psychological impact, and the implications of a hereditary disease for his or her family. The effectiveness of the available treatment options with their limitations and risks can be discussed. Issues of employment and insurance can also be addressed along with any other concerns of the patient. Genetic counseling appears to be the best method to deal with the potential for denial or noncompliance and prevents the bad outcomes that can result from delays in evaluation and treatment.

Genetic Testing

APC protein truncation testing takes advantage of the observation that most significant *APC* mutations result in a truncated *APC* protein. This truncated protein can be identified in 80% of FAP families[90] but does not identify the actual mutation and should not be used to exclude FAP if other clinical information supports the diagnosis of FAP or its variants.

Direct evaluation of the *APC* gene using DNA sequencing technology is now commercially available. This technology allows for the identification of the actual mutation in 87% of patients with FAP.[91] While genotype–phenotype correlation is not perfect, it does have sufficient predictive power to be useful in the selection of appropriate screening examinations and therapeutic modalities.[92,93] Again, the absence of a detectable abnormality should not be used to exclude FAP if other findings support the diagnosis of FAP.

Once an abnormality is identified by either protein truncation testing or direct mutation analysis of the *APC* gene in a family, the accuracy of the test for other family members approaches 100% and can be used to exclude FAP in at-risk family members.

Screening

While observational studies of families with FAP suggest a trend toward an earlier stage of disease and a probable reduction in colorectal cancer mortality with screening,[94,95] there are few published, randomized, controlled trials of screening programs in people with an increased risk of colorectal cancer due to a genetic cause. Therefore, recommendations regarding screening of these patients cannot be based

on strong evidence of effectiveness, but instead on clinical judgment, taking into account the biologic and clinical behavior of FAP and AAPC as well as possible parallels with nonpolyposis patients for whom screening is known to be effective in reducing the risk of dying from colorectal cancer. Expert groups with an interest in FAP have used this method to develop the guidelines for screening patients at risk for this condition (Table 6.5).

For the nonpolyposis patient, fecal occult blood testing and double-contrast barium enema have both been shown to be useful in decreasing mortality from colorectal cancer. Endoscopy, however, is the screening procedure that is uniformly chosen by expert groups for patients with FAP. Adenomatous polyps will develop in 15% of patients with FAP by age 10. This increases to 50% at age 15 and 75% by age 20. Colorectal cancer will have developed in 7% of patients with FAP by age 21 and in 50% by age 39.[43,96–98] Screening endoscopic examination should therefore begin at age 12.

There is an apparent predilection for rectal and left colonic polyps in FAP that has led some to recommend flexible sigmoidoscopy as the endoscopic procedure of choice for screening.[41] Others have recommended colonoscopy as the initial examination.[99] Most agree that, after the initial examination, annual sigmoidoscopy should be performed until polyps develop for those whose family history or genetic test results suggest FAP. This should be continued until age 50 to 60 for patients at risk for inheriting an *APC* mutation who decline genetic testing or have an indeterminant test result. If no polyps have developed by that age, it is reasonable to conclude that these patients did not inherit the gene defect. Screening should be continued lifelong for patients who are found to have an *APC* mutation by genetic testing. Individuals at risk for FAP who undergo genetic testing and are found to be definitively mutation negative do not need annual screening, although most would recommend a baseline endoscopic examination at age 18 to 21 to reduce the possibility of a false negative genetic test result.[97]

While attenuated FAP (AAPC), like classic FAP, is associated with *APC* mutations and ultimately results in colorectal cancer, the clinical

Table 6.5 Screening recommendations for patients at risk for FAP.

For the patient with suspected FAP
Flexible sigmoidoscopy or colonoscopy at age 12
Annual sigmoidoscopy until age 60
For the patient with suspected AAPC
Colonoscopy every 1–2 y
Begin at age 18–21
For the patient with a risk of desmoid tumors
Annual computed tomography for 3–5 y following pregnancy, abdominal trauma, or surgery
For the patient at risk for gastroduodenal polyps
Endoscopy (EGD)
Begin when colon polyps found
Every 1–3 y

pattern is different, with the polyps more likely to be right colonic and develop 10 to 20 years later in life. The development of colorectal cancer is also delayed 10 to 20 years.

For individuals whose family history or *APC* gene abnormality suggests AAPC, colonoscopy is the screening procedure recommended.[99] Screening should begin at age 18 to 20 and continue every 1 to 2 years. There is no consensus on when to discontinue screening, but given the natural history of AAPC it would seem that screening of the healthy patient should continue into the eighth decade of life.

Once a patient is known to have an *APC* mutation, by either genetic testing or clinical manifestations of FAP, it can be anticipated that gastroduodenal neoplasia will develop in 80% to 90%.[46,94] While this neoplasia can progress to carcinoma, this is uncommon, occurring in 11% with 7 years follow-up.[47,48] Esophagogastroduodenoscopy (EGD) is used to screen the upper GI tract. Again, there is no consensus on when to begin or how frequently screening is needed, but it seems reasonable to begin screening between age 20 to 25 with an interval of 1 to 5 years between procedures dependent on the endoscopic findings.

While there are numerous other extracolonic manifestations of FAP, screening does not seem warranted for benign problems such as CHRPE and osteomas. It would appear reasonable, however, given the potential for aggressive behavior of intraabdominal desmoids, to screen by abdominal computerized tomography for the development of these lesions in patients whose *APC* mutation or family history suggest a propensity for these tumors, in particular after an abdominal surgical procedure. Screening for hepatoblastoma or the malignant CNS tumors associated with Turcot syndrome cannot be justified in the patient without a family history of these problems.

Management of Intestinal Polyps

Chemoprevention

Several randomized controlled trials have shown that the NSAIDs sulindac, celecoxib, and aspirin reduce the number and size of colorectal adenomas in patients with FAP.[32,100–103] These drugs may possibly act through cyclo-oxygenase II inhibition or by triggering programmed cell death.[104] What is unclear is if suppression of the polyps will prevent the progression to colorectal cancer. In nonpolyposis patients, aspirin does not appear to decrease the incidence of colorectal cancer,[105] and there have been case reports of cancer occurring in patients with FAP whose polyps were suppressed with sulindac.[101,106] Nonsteroidal anti-inflammatory drugs, with the possible exception of celecoxib,[107] are ineffective for the suppression of duodenal adenomas.[108,109] Other agents that have been reported to decrease the incidence of colorectal adenomas or carcinomas in observational studies include folic acid supplements,[110] calcium supplementation,[111] and estrogen.[112–114] These studies, however, do not specifically include data about individuals with an inherited propensity for colorectal cancer.

With the data and medications currently available, chemoprevention cannot be recommended as primary therapy for intestinal polyposis

but instead should be reserved for the special circumstance where surgical therapy is declined or has an excessive risk of complications. It may, however, have a role in the treatment of adenomas that develop in the ileal pouch after proctocolectomy with either ileal pouch–anal anastomosis or continent ileostomy construction.

Surgical Therapy

While surgical intervention is the primary therapeutic modality for the intestinal manifestations of FAP, there are still many decisions, such as the timing of surgery and the surgical procedure to be performed (Table 6.6). These decisions frequently involve adolescents and their parents and can only be made after careful consideration of the emotional maturity of the patient and all the data obtained from examination of the phenotype, genotype, and family medical history. Although colorectal cancer is unusual before age 20,[98] the risk is doubled for patients with more than 1,000 polyps when compared to those with fewer than 1,000.[115] The site of the *APC* mutation can also be used to predict the severity of the disease and risk of colorectal cancer at a young age. Mutations between codons 1,250 and 1,464, but in particular at codon 1,309, are associated with a more aggressive phenotype and a larger number of polyps.[92,93,116,117] In contrast, mutations before codon 157 are associated with a milder phenotype (AAPC) and a low risk of colorectal cancer before age 21.[13,18] This has led to the recommendation that patients with a likelihood of aggressive disease, as indicated by either clinical examination or genetic findings, undergo surgery at a convenient time in their early to midteen years, while those with less severe disease may delay surgery until their late teens or early 20s.

Phenotypic and genotypic features, in addition to the family medical history, are also important in the selection of the optimal surgical procedure. The main surgical options include total abdominal colectomy with ileorectal anastomosis (IRA), proctocolectomy with ileal pouch–anal anastomosis (IPAA), and total proctocolectomy with ileostomy (TPC). Each of these procedures has advantages, disadvantages, and risks. Also, there are options in the technical performance of each procedure that must be considered. The number of options available is testimony to the fact that no one procedure is ideal for all

Table 6–6. Surgical management of FAP and AAPC.

Abdominal colectomy with ileorectostomy
Attenuated FAP by family history or genetic testing
Mild FAP as manifested by fewer than 20 polyps in the rectum and less than 1,000 overall
Proctocolectomy with ileal pouch–anal anastomosis
Severe disease by family history, clinical findings, or genetic test results
Cancer in the colon or mid- to upper rectum
Risk of desmoid tumor
Proctocolectomy with end or continent ileostomy
When ileal pouch–anal anastomosis is contraindicated because of anal sphincter dysfunction or technical problems
Low rectal cancer that precludes sphincter preservation

patients, and the surgical procedure chosen should be individualized for each patient.

Minimally Invasive Surgery: Minimally invasive surgical techniques have been reported to result in decreased pain and hospital stay, sooner return of bowel function and return to preoperative activity, and improved cosmetic results. Recent randomized controlled trials have suggested that the benefits of minimally invasive surgery may be less than previously reported. This controversy is outside the scope of this chapter, but suffice it to say that laparoscopic-assisted surgery may be more acceptable to the young asymptomatic patients with FAP.

Total Abdominal Colectomy with Ileorectal Anastomosis: The advantages of IRA include a low surgical complication risk, restored GI continuity, and superior results in terms of bowel function.[118,119] Significant surgical complications will occur in 11% of patients after IRA, with a mortality rate of 1.6%.[120,121] Preservation of the rectum avoids the potential of damage to the pelvic nerves, which can occur during removal of the rectum and result in severe urinary and sexual dysfunction.[122,123] While this complication is rare, it can be catastrophic in the young, active asymptomatic patient.

While not all agree, there seems to be better bowel function after IRA when compared to IPAA. The number of bowel movements in 24 hours and at night is less for IRA than for IPAA, with greater ability to defer bowel movements and better continence.[118,119,121] These conclusions are influenced by the length of the remaining rectum. Better bowel function is achieved with a longer rectal remnant but has an associated increased risk of subsequent rectal neoplasia. It appears that 10 to 12 cm of remaining rectum provides an adequate fecal reservoir for acceptable bowel function without an undue risk of subsequent proctectomy for neoplasia.[53,124]

The potential for polyps and cancer to develop in the remaining rectum is the major disadvantage of IRA. There is considerable controversy regarding the frequency of carcinoma arising in the rectal remnant, but it is probably 25% to 37% over 20 years.[53,124,125] The clinical manifestations of the disease can provide prognostic information regarding the potential for subsequent development of carcinoma in the remaining rectum. The presence of more than 20 polyps in the rectum or a rectal polyp larger than 3 cm are associated with an increased risk of cancer in the rectal remnant. The presence of a cancer or greater than 1,000 polyps in the colon is also predictive of an increased risk.[126]

Genetic factors may also be used to predict the likelihood of a cancer developing in the remaining rectum. A mutation located between codons 1,250 and 1,464 is associated with a larger number of polyps,[92,93,116,117] which would suggest an increased risk of subsequent rectal cancer, while a mutation before codon 157 is associated with fewer rectal and colonic polyps[13,18] and a low cancer risk in the remaining rectum.[126]

Another disadvantage is the potential need for further abdominal surgery. In addition to the 25% to 37% risk of developing a rectal neoplasm over a 20-year period following IRA,[53,125] 11% of patients will

have a proctectomy for benign reasons such as multiple large adenomas or incontinence.[124]

The potential also exists for an intra-abdominal desmoid tumor to develop following the initial operative procedure and limit the surgical options available.[127,128] It would seem prudent to avoid IRA in patients whose family medical history suggests a propensity for desmoid tumors or whose *APC* abnormality is located between codons 1,403 and 1,578.

Proctocolectomy with Ileal Pouch Anal Anastomosis: Proponents of IPAA as the procedure of choice for most patients with FAP base their recommendation on the risk of cancer in the remaining rectum after IRA and comparable bowel function and quality of life for IPAA and IRA.[123,129,130] The details of these issues are included in the discussion of IRA. Differences in the technique of IPAA make it difficult to conclusively resolve these concerns. While adenomas in the rectal remnant are the major disadvantage of IRA, preservation of the anal transitional zone in IPAA is associated with a 30% risk of neoplasia in the area.[131,132] Removal of this area by rectal mucosectomy will decrease this risk significantly[132,133] but not remove it entirely, and this procedure is associated with diminished bowel function and an increased incidence of surgical complications.[134,135]

The higher surgical complication risk is the major disadvantage of IPAA. The overall results of IPAA have been reported from most large North American and European centers. In general, the operative mortality after IPAA is similar to that of IRA, being 1% to 2%[136–138] with major postoperative complications occurring in 21% to 40%.[136,139,140] Reoperation is required in 16% to 30% of patients, with excision of the ileal pouch being required in 3% to 12%.[136,138,139] One possible complication that needs special mention is pelvic sepsis. Despite routine use of a diverting ileostomy, it has a reported incidence of 7% and is predictive of a poor functional outcome.

Another potential problem is pouchitis, which is common in patients with inflammatory bowel disease but unusual in those with IPAA for FAP.[141] Other problems that can lead to pouch failure include ischemia, poor pouch emptying, soiling, or incontinence, but these are uncommon. In the absence of surgical complications that impair pouch function, patients can expect functional results comparable to IRA for many years.[138,140]

The need for temporary fecal diversion and a second surgical procedure to close the stoma is another perceived disadvantage of IPAA. The lower risk of anastomotic complications associated with preservation of the anal transition zone may allow omission of the diverting ileostomy in selected patients and permit a one stage procedure.[134,135,142]

Another potential problem related to proctectomy is damage to the pelvic sympathetic and parasympathetic nerves, resulting in urinary and sexual dysfunction. For males the predominant problems are impotence and retrograde ejaculation, with a reported incidence of 2% and 6%, respectively.[143] Sexual dysfunction is more common in women, occurring in 25% to 30%. The main problems are vaginal dry-

ness and dyspareunia.[143,144] Another recognized problem after pouch surgery in women is infertility, with occlusion of the fallopian tubes occurring in 10% of women.[143,145]

Temporary urinary retention occurs in 12% of patients[146] following IPAA, but most studies report no long-term urinary disturbance.

Total Proctocolectomy: Although almost never performed as the initial procedure for FAP, TPC has some advantages that make it attractive. The risk of neoplasia associated with IRA and IPAA with preservation of the anal transition zone is avoided, as is the risk of anastomotic leakage. There is, however, the potential for damage to the pelvic nerves and the risk of a persistent perineal sinus. The risk of damage to the pelvic autonomic nerves with resultant sexual and urinary problems is related to the extent of the pelvic dissection and may be as high as 70% with radical oncological procedures.[146,147] If, however, a rectal mucosectomy or intersphincteric dissection can be utilized to remove the distal rectum, incidence of these problems is no greater than that reported for IPAA.

Another problem unique to TPC is the possibility of a persistent perineal sinus. Again, the incidence of this problem is related to the extent of the perineal excision and may be as high as 16% following abdominal perineal resection for cancer.[148,149] The risk of this problem can also be minimized by use of an intersphincteric dissection or rectal mucosectomy to remove the distal rectum.[150,151] There is, however, a small risk of incomplete removal of the rectum with rectal mucosectomy and intersphincteric dissection, and the possibility of carcinoma developing in the retained segment.

The overwhelming disadvantage of TPC is the resultant permanent ileostomy.[152] With preoperative counseling, proper selection of the stoma site, and postoperative teaching, the patient with an ileostomy can lead a full and active life. The difficulty of convincing a young, asymptomatic patient of undergoing ileostomy may actually lead to surgical delay and the potential for carcinoma to develop. One possible option for these patients is the construction of a continent ileostomy.[153] This procedure was more common prior to the development of IPAA and now is performed in only a few centers. The major criticism of the continent ileostomy is the surgical complication rate, which is reported to be 36% with a 1.2% mortality.[154] The most common problems are intestinal obstruction, pouch perforation with either fistula formation or sepsis, and nipple valve failure. Revision of the pouch will be required in 22%.[155,156] Despite these setbacks, eventual continence will be achieved in over 90% of patients.[154–156] As with IPAA, pouchitis is another problem associated with the continent ileostomies and is common after procedures for inflammatory bowel disease and unusual in patients whose ileostomy was constructed following TPC for FAP.[153,157,158] Patients with a continent ileostomy have an improved quality of life compared to a conventional ileostomy, and this procedure has been recommended for patients with a poor functional outcome following IPAA.[158,159]

Currently, TPC is chosen when a proctectomy is needed, but there is a contraindication to sphincter preservation such as a low rectal can-

cer, poor sphincter function from prior anorectal conditions or obstretic trauma, or a technical problem that prevents the ileal pouch from reaching the pelvic floor.

Postoperative Surveillance: Regardless of the surgical procedure chosen, postoperative surveillance of the rectum following IRA, the ileal pouch after IPAA, the ileostomy after TPC, and for the extracolonic manifestations of FAP is essential for the remainder of the patient's life. The potential for rectal neoplasia following IRA and IPAA with preservation of the anal transition zone was included in the discussions of those procedures. Endoscopy of the rectal remnant should be performed annually to evaluate any polyps that remain in the rectal remnant and monitor for the development of any additional lesions. Spontaneous regression of rectal polyps has been reported after IRA in 67% of patients for a duration of up to 4 years.[160,161]

Most authors would agree that polyps smaller than 5 mm should be followed while larger adenomas should be removed without fulguration. Rectal scarring from repeated polyp fulguration over many years can make cancers flat and difficult to identify. The accumulated rectal scarring can also reduce the compliance of the rectum with an increased stool frequency and urgency and decreased continence. In one study, the most common reason for proctectomy after IRA was incontinence and rectal stricture.[124] The chronic scarring may also make subsequent proctectomy, if needed, difficult and preclude conversion to an IPAA. Proctectomy should be considered with increasing size and numbers of polyps or with the development of severe dysplasia. In the absence of contraindication, technical problems, or ileal polyps, IPAA is an acceptable alternative with functional results almost as good as IPAA performed as the initial procedure.[162]

Adenomas and carcinomas have also been described in the ileal pouch after IPAA[163–165] and in the conventional or continent ileostomy after TPC.[166–169] The incidence of pouch polyposis following IPAA has been reported to be 42% after 7 years.[170–172] Most experts recommend the NSAIDs sulindac or celecoxib for the management of ileal pouch adenomas even though they have limited efficacy in duodenal adenomas.[107,109] The significance of pouch polyposis is uncertain and will remain so until the cohort of patients with FAP treated with IPAA have a mean follow-up of at least 20 years.

Duodenal Adenomas

The incidence of duodenal adenomas in patients with FAP approaches 90%, with 11% developing severe dysplasia after 7 years[44,46,94] and cancer arising in 12% an average of 16 years following colectomy.[47,48] The consensus among authorities is that the role of endoscopy is to detect severe dysplasia, not eradicate the polyps. Small adenomas with low grade dysplasia may be biopsied and followed, while polyps larger than 1 cm or those with severe dysplasia should be treated. With the possible exception of celecoxib,[107] NSAIDs are ineffective for the suppression of duodenal adenomas. Endoscopic or surgical excision is the preferred choice for managing large or dysplastic duodenal adenomas. However, recurrence is likely after endoscopic removal[71,173–175]

and should be considered only when the risk of more definitive surgery is unacceptably high. Pancreaticoduodenectomy and pancreas-preserving duodenectomy have both been reported to have a low risk of surgical complications and a low polyp recurrence rate.[176–178] The surgical results for patients who develop invasive malignancy are poor, with recurrence of the cancer and death as the usual outcome.[47]

Desmoid Tumors

Desmoid tumors are proliferative, locally invasive, nonmetastasizing fibromatous tumors with a reported incidence of 12% to 38% in patients with FAP.[57–60] Desmoid tumors associated with FAP are intra-abdominal in 80% and in the abdominal wall in 18%.[57,60] They often present within 3 years of an abdominal surgical procedure.[179] The natural history of intra-abdominal desmoids is variable and can include stability periods of rapid growth and resolution or, rarely, sustained aggressive growth.[42]

Many agents have been utilized in patients with desmoid tumors with varying success. The objective response rate to NSAIDs is about 50%, and response may take a long time to achieve.[180] Estrogen receptors can be identified in 40% of desmoid tumors. Estrogen blockade using tamoxifen or toremifene will lead to a positive result in 50% of patients.[61,66] Other agents reported to be effective include corticosteroids,[181] warfarin,[182] interleukin-2,[183] and interleukin alpha.[184]

Various cytotoxic regimens have been utilized for aggressive desmoids and show some promise. The combination of vinblastine and methotrexate can be effective and has a low toxicity.[185,186] The response to doxorubicin and dacarbazine is much more dramatic, but the toxicity of this regimen may limit its use.[187–190] An algorithm for the management of intra-abdominal desmoid tumors is shown in Figure 6.2.

Intra-abdominal desmoids are usually at the base of the mesentery, intimately involving the blood supply for large segments of the small intestine. Attempts to remove these tumors surgically is reported to have a perioperative mortality of 10% and higher and a major morbidity of 20% or more.[191,192] Recurrence following surgery is also common, occurring in 65% or more of patients.[42,192,193] Most authorities recommend that surgery be reserved for the 27% of patients who will develop complications of intra-abdominal desmoids such as obstruction of the intestine or ureters or ischemia of the bowel.[42,59,192,194] A recent report of small intestinal transplantation in a patient with an intra-abdominal desmoid[195] is testimony to the extent of surgery needed to remove these tumors and may provide another surgical option in the future.

Abdominal wall desmoids are usually smaller and more circumscribed than intra-abdominal desmoids and without the anatomic constraints to surgical excision. Although not all would agree, most experts would excise abdominal wall desmoids with a 1- to 2-cm margin of healthy tissue whenever possible.[42,192] The risk of recurrence after excision is less than that for intra-abdominal desmoids, and the operative morbidity is less even though the large abdominal wall defects that result can be challenging to repair.

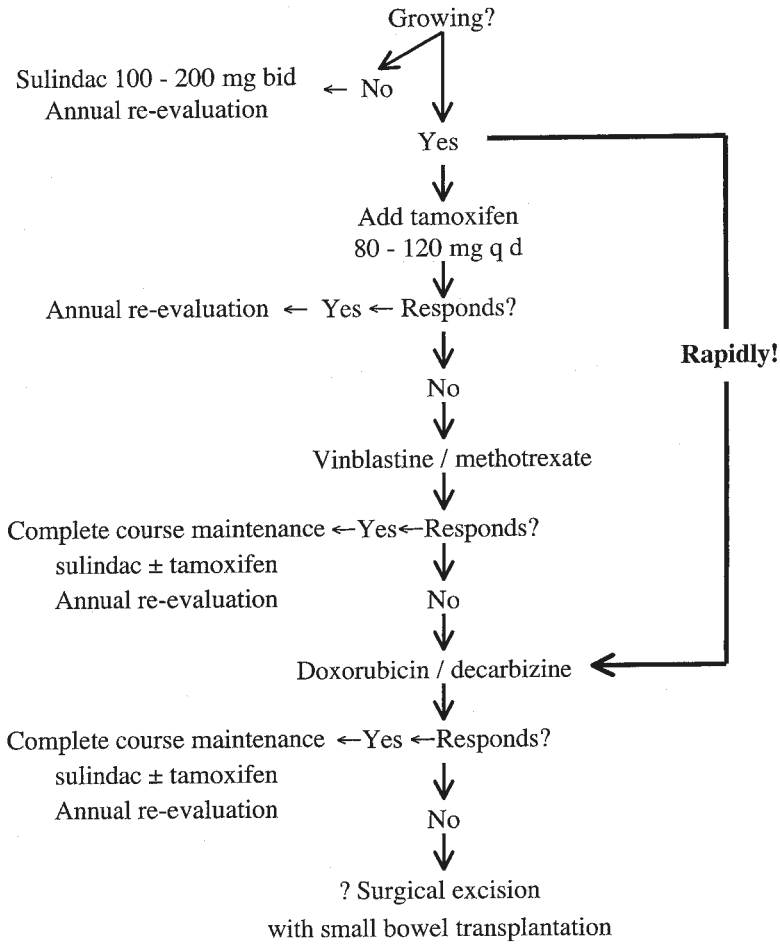

Figure 6.2 Management of intra-abdominal desmoid tumors.

Peutz-Jeghers Syndrome

Clinicopathologic Features

The rare syndrome of GI polyps with associated pigmentation of the oral cavity was first described by Peutz in 1921[196] with several additional patients reported by Jeghers in 1944.[197] Although PJS is almost invariably familial, transmitted in an autosomal-dominant manner, sporadic cases do occur.[198] Abnormalities of the serine threonine kinase gene, *SKTII*, located at chromosome 19p 13.3 has been identified as the etiology of the PJS.[33] The disease occurs equally in males and females, and while it may present in childhood or adolescence, it is usually diagnosed in the third decade of life.[199]

Gastrointestinal Polyps

The most frequent location of the polyps in PJS is the proximal small intestine, with polyps of the stomach or colon much less common.[199]

The polyps are usually pedunculated with short broad stalks but may be sessile. They vary in size from 3 mm to 3 cm and grossly resemble adenomas. Microscopically, the polyps are covered by histologically normal epithelium with no glandular irregularity or nuclear hyperchromasia. The polyps have a core of muscular tissue derived from the muscularis mucosa without the excess lamina propria associated with juvenile polyps. They are considered to be true hamartomas produced by an overgrowth of the muscularis mucosa.[40] The malignant potential of the polyps is controversial. While hamartomas are not believed to have malignant potential, transformation of hamartomas into adenomas and adenocarcinoma have been demonstrated.[200,201] Multiple studies have shown a high relative risk of both intestinal and extraintestinal malignancies in patients with the PJS.[202–204]

Cutaneous Manifestations

The pigmentation associated with PJS consist of 1- to 2-cm diameter, black or dark brown, freckle-like lesions located on the lips and buccal mucosa most commonly, but also on occasion on the hands and feet. The skin findings occur during childhood and may resolve after puberty.

Other Tumors

There is an apparent increased risk of other malignancies in patients with PJS. Women have been reported to be more likely to develop ovarian sex cord tumors of the annular tubules, adenoma malignum of the cervix,[205,206] and breast cancer.[207] Men have a higher incidence of feminizing Sertoli cell tumors of the testis,[208] and both genders have an increased risk of pancreatic cancer.[202,203]

Diagnosis and Evaluation

Clinical symptoms associated with PJS include anemia and abdominal pain. Anemia is the result of occult bleeding from the polyps while major bleeding episodes may result from torsion and autoamputation of a polyp. The polyp may also predispose to intussusception of a segment of intestine. This is usually intermittent, occurring after meals and causing severe colicky abdominal pain. On occasion, the intussusception will result in intestinal obstruction requiring surgical intervention. Once the diagnosis is suspected from the family medical history, clinical symptoms, and physical findings, endoscopy is the procedure of choice to confirm the diagnosis. On occasion, radiological contrast studies are needed to evaluate areas of the small bowel that cannot be reached by endoscopy.

Management

Genetic Counseling

As with all inherited cancer syndromes, the initial step in management is genetic counseling once the diagnosis is suspected or confirmed. Genetic counseling has been discussed elsewhere, but suffice it to say that its importance cannot be overstressed.

Table 6.7 Surveillance guidelines for PJS.

Site	Procedure	Onset (y)	Interval (y)
GI tract	Upper and lower endoscopy	10	2
	with small bowel follow-through	10	2
Breast	Breast examination, mammography	25	1
		25	2–3
Testicle	Testicular examination	10	1
Ovary, uterus	Pelvic examination, pelvic	20	1
	ultrasound	20	1
Pancreas	Endoscopic ultrasound (if available) or abdominal ultrasound	30	1–2

Intestinal Polyps

Even more so than for FAP, there are no large studies that demonstrate efficacy of any treatment strategy or an advantage of one regimen over another. The surveillance recommendations (Table 6.7) are based on information about the natural history of PJS and the known risks. Currently, upper and lower endoscopy is recommended every 2 years beginning at age 10, with polyps larger than 5 mm being removed to hopefully prevent bleeding complications, intussusception, and malignant change.[209,210] Polyps larger than 1.5 cm that cannot be removed endoscopically should be removed surgically through an enterostomy. If surgical intervention is necessary, a combined endoscopic and surgical approach should be utilized with the goal of removing all small bowel polyps. The removal of segments of small intestine should be avoided, if possible, because the majority of the small bowel is usually affected, and polyp formation will progressively decline after 30 years of age.[199,211,212] On occasion, surgical therapy will be necessary for intestinal hemorrhage or obstruction. In this circumstance, removal of all polyps and the avoidance of intestinal resection should still be attempted if the situation allows. A more aggressive surgical approach with adherence to oncological principles will be needed for those with malignant lesions.

There is no consensus regarding screening recommendations for the other tumors associated with PJS other than to emphasize the importance of complying with the usual recommendation for periodic gynecologic and breast examinations and the prompt evaluation of any testicular mass.

Juvenile Polyposis Syndromes

Clinicopathological Features

The presence of multiple juvenile polyps in the GI tract is now known to be a feature of several rare syndromes. In the past, these syndromes were grouped together, and only recently has it been recognized that they are distinct entities with different etiologies and natural histories. Initially, juvenile polyposis was thought to be the result of an abnor-

mality of a protein tyrosine phosphatase (*PTEN*) gene located on chromosome 10q23. It is now recognized that this is the etiology of Cowden's disease and the Bannayan-Riley-Ruvalcaba (BRR)[34,213,214] syndrome. Currently, an abnormality in the gene for a transforming growth factor-B intracellular signaling molecule, Smad4, located on chromosome 18q21.1 is thought to be responsible for juvenile polyposis.[35,36] While these syndromes may arise de novo in one third of patients, they are usually familial with an autosomal dominant pattern of inheritance. These syndromes usually present in the first decade of life with a peak incidence at age 2 to 5.

Gastrointestinal Polyps

In the majority of patients with juvenile polyposis, the polyps are limited to the colon, although they can involve any portion of the GI tract. Histologically, the polyps are hamartomas with a distinctive cystic architecture, mucus-filled glands, and an expanded lamina propia with a dense infiltration of lymphocytes, eosinophils, and neutrophils.[215] The polyps range in size from 5 to 50 mm.

Extraintestinal Manifestations

Extracolonic abnormalities have been reported in patients with juvenile polyposis, but these most likely represent misdiagnosed Cowden's disease or BRR syndrome. The GI polyps are considered minor criteria for the diagnosis of Cowden's disease and are present in only 40% of patients.[216] Hamartomas of the skin, breast, thyroid, and brain are characteristic features of Cowden's disease. Other common lesions include oral papillomas, facial trichilemmomas, fibromas, and hemangiomas.[213]

Intestinal hamartomas are also found in approximately one half of patients with BRR syndrome. Components of BRR syndrome also include subcutaneous and visceral lipomas and hemangiomas, lipid storage myopathy, developmental delay, and seizures.[217]

Diagnosis and Evaluation

While the potential for juvenile polyposis is suspected from the family history, most affected individuals are diagnosed after the onset of symptoms. Painless rectal bleeding is the most common presenting complaint. Abdominal pain and iron deficiency anemia are also common clinical findings. On occasion, patients may present with colon–colonic intussusception and intestinal obstruction.[218] Endoscopy is preferred over contrast radiological evaluation as it is both diagnostic and therapeutic.[219]

Juvenile polyps occur in 1% to 2% of asymptomatic children, with 50% of these children having more than one and 20% having five or more.[220,221] The risk of colorectal cancer in patients with juvenile polyps has not been resolved. There is no increased risk in patients with a solitary lesion,[222] while at the other end of the spectrum is the 50% cancer risk in the patient with juvenile polyps and a family history of col-

orectal cancer.[223–225] Attempts have been made to distinguish between polyps throughout the GI tract, generalized juvenile polyposis; three or more polyps limited to the colon, juvenile polyposis coli; and juvenile polyps in a patient with a family history of juvenile polyps or colorectal cancer, familial juvenile polyposis.[219] Each of these has been associated with an increased cancer risk.[223,225]

Children with Cowden's disease or BRR syndrome usually present with the extraintestinal manifestations of these diseases. The evaluation of these conditions is directed at the identification of all affected sites.

Management

Genetic Counseling

As with all diseases with a genetic aspect, the initial step in the management of patients with a juvenile polyposis syndrome is genetic counseling. This crucial component has been discussed in detail in chapter 1 and will be not be addressed here other than to reassert its importance.

Treatment

There is no consensus regarding screening or treatment recommendations for patients with juvenile polyposis syndromes. It is unknown if removal of the juvenile polyps decreases the incidence of colorectal cancer or if screening will change the natural history of the disease. Taking into account the risk of bleeding, iron deficiency anemia, and intussusception, it would seem prudent to remove all polyps endoscopically if possible. Should surgical intervention be required, a combined approach with endoscopy, as is performed with PJS, may be considered.

It is clear that the risk of cancer associated with the juvenile polyposis syndromes justifies a lifelong surveillance program. With the average age at diagnosis of an overt neoplasm being 35,[223] this program should probably begin in the teenage years. Colonoscopy is preferred, with upper endoscopy and radiographic examination of the small intestine added for those with generalized juvenile polyposis. The interval between examinations is debatable but probably should vary between 2 to 5 years based upon the age of the patient, the family history, and the findings of previous examinations.

The primary cancer risk for patients with Cowden's disease is for breast and thyroid malignancies.[219] There are no special recommendations regarding screening for these cancers other than to emphasize adherance to established programs for the detection of breast and colorectal tumors and the prompt evaluation of any neck or male breast masses.

The BRR syndrome does not appear to have an associated increased risk of malignancy.[219] Special cancer screening programs for these patients are not warranted.

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7

Hereditary Nonpolyposis Colorectal Cancer

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Colorectal cancer is a major public health concern in westernized societies. In the United States alone it is one of the major causes of cancer death in both men and women with approximately 140,000 new cases each year and almost 50,000 deaths.[1] It is estimated that approximately 10% of these cases are the result of a primary germline genetic mutation.[2–5] There are two major inherited colorectal cancer syndromes: familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer syndrome (HNPCC). Familial adenomatous polyposis is thought to account for less than 1% of colorectal cancer cases while HNPCC is thought to be responsible for approximately 5% to 8%.

Hereditary nonpolyposis colorectal cancer, or Lynch syndrome, is an autosomal dominant genetic disorder. The genetic basis for the disorder is a germline mutation of mismatch repair (MMR) genes. While mutations in at least six MMR genes have been implicated, mutations at *hMSH2* and *hMLH1* account for 40% and 35% of the mutations, respectively. By virtue of inheritance, affected individuals are at an increased risk of developing colorectal cancer or certain extracolonic cancers at an early age. Based on multiple published studies, the International Collaborative Group on HNPCC set forth clinical criteria (Table 7.1) for the diagnosis of HNPCC in the absence of polyposis in 1999.[6–11]

History

The story of HNPCC starts at the end of the 19th century in Ann Arbor, Michigan, when the professor of pathology at the University of Michigan, Aldred S. Warthin, questioned his seamstress as to the cause of her depression. She offered that she feared death at an early age from gastric, colon, or uterine cancer, as many of her ancestors had suffered this fate. His seamstress did in fact die at an early age of endometrial cancer. Wartin described his seamstress's family in an article published in 1913. He called this family "G" for its German roots.[12]

Table 7.1 Features of HNPCC (Lynch syndrome).

Familial clustering of colorectal and/or endometrial cancer
Associated cancers: cancer of the stomach, ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract, and skin (sebaceous tumors)
Development of cancer at an early age
Development of multiple cancers
Features of colorectal cancer: (1) predilection for the proximal colon; (2) improved survival; (3) multiple colorectal cancer; (4) increased proportion of mucinous tumors, poorly differentiated tumors, and tumors with marked host-lymphocytic infiltration and lymphoid aggregation at the tumor margin
Features of colorectal adenoma: (1) the numbers vary from one to a few; (2) increased proportion of adenomas with a villous growth pattern and (3) a high degree of dysplasia; (4) probably rapid progression from adenoma to carcinoma
High frequency of MSI (MSH-H)
Inmunohistochemistry: Loss of *MLH1*, *MSH2*, or *MSH6* protein expression
Germline mutation in MMR genes (*hMSH2*, *hMLH1*, *hMSH6*, *hPMS1*, *hPMS2*)

This information was not used until 1962, when Henry T. Lynch was consulted by a gastroenterologist regarding a patient with a strong family history of colorectal cancer. In the absence of multiple colorectal polyps, the presumed diagnosis of FAP proved incorrect. Studying the family tree, Lynch found that the family had a high incidence of not only colorectal cancer but other extracolonic tumors, especially endometrial cancer. The patient ultimately died of an adrenal cortical carcinoma.[13]

Lynch presented this case in 1964 at a meeting of the American Society of Human Genetics. Marjorie Shaw from the University of Michigan, who was in attendance, was reminded of a similar family that she knew. Lynch and Shaw conferred, and in 1966 Lynch published an article on these two families, calling them "N" (Nebraska) and "M" (Michigan). These families were of great interest because they had a wide anatomic distribution of malignant lesions, there were family members with multiple primary tumors, and they had a high incidence of endometrial cancer. Pedigree findings indicated an autosomal dominant inheritance pattern, and the families had similar ethnic origins. The term "cancer family syndrome"[14] was coined.

Curiously, the proband of family "N" was quoted as saying, " . . . everyone in the family dies of cancer . . . ," reminiscent of Warthin's seamstress.

The chairman of pathology at the University of Michigan, Warthin's successor, A. James French, on learning about families "N" and "M" was reminded of family "G," on which he had 30 years of detailed data. This material was put at Lynch's disposition, and after continued investigation of family "G" he published an updated review in 1971. In this article, he noted the autosomal-dominant inheritance

pattern and a predominance of colonic, endometrial, and gastric adenocarcinomas.[15]

In the mid-1980s, as similar pedigrees were recognized and reported, the name cancer family syndrome was changed to hereditary nonpolyposis colorectal cancer. This term was chosen to emphasize the lack of multiple polyps that differentiated it from the polyposis syndromes.[16]

In 1984, Boland and Troncale[16A] described two patterns of this syndrome, calling them Lynch I and Lynch II. Lynch I families had predominantly colorectal cancer, and Lynch II families had colorectal cancer and extracolonic tumors, primarily tumors of the female genital tract.[16]

A linkage approach was used to determine the predisposing locus of HNPCC. In 1993, after a search involving almost the entire human genome, Peltomaki et al. reported an unequivocal linkage to chromosome 2p in two large HNPCC kindreds.[17] They then tested loss of heterozygosity for 2p markers because a tumor suppressor gene was thought to cause the cancer predisposition in the families.[18] While this theory did not prove true, most of the familial cancers were found to have widespread alteration in short repeated DNA sequences, suggesting the numerous replication errors (RER's) had occurred during tumor development. Lindblom et al. almost simultaneously employed a combined approach with microsatellite markers and restriction fragment length polymorphisms and linked cancer occurrences in HNPCC with mutations on chromosome 3p.[19]

Most colorectal cancers from HNPCC patients have microsatellite instability, and the term "replication error positive" is used to describe these tumors. It is thought that the HNPCC gene is a human homolog of DNA mismatch repair genes that have been described in yeast and bacteria.[20] Fishel et al., using information about the location and function of the susceptibility gene on chromosome 2p, isolated the human homolog of the yeast *MSH2* (MutS homolog 2) by virtue of sequence homology between species.[21] Evidence that *hMSH2* was the correct gene came when germline mutations of *hMSH2* were found to segregate with cancer in three large HNPCC families.[22] Within 1 year the mutL homolog was cloned on chromosome 3p21.[23] Since that time, eight additional mutL homologs (*hPMS1*) and MutS homolog have been identified. These genes are discussed further below.

Clinical Features

Lynch syndrome I families have a site-specific, autosomal-dominant inherited susceptibility to colorectal cancer. While ~90% of sporadic colorectal cancers occur in patients older than 50 y, the average age of cancer diagnosis in Lynch I patients is 44 y. With sporadic colorectal cancers, about 70% of tumors are located distal to the splenic flexure. In HNPCC, about 70% of the tumors arise proximal to the splenic flexure, primarily in the right colon. Lynch I patients have an increased incidence of synchronous colon cancers. This 7% risk of synchronous cancer is about three times higher than that seen in patients with sporadic colorectal cancer. There is also an increased incidence of

metachronous tumors, about five to seven times that of the general population.[24] Thirty percent to 50% of patients treated with segmental resection develop a metachronous tumor within 10 to 15 years of resection.[25,26] Even in patients treated with a total abdominal colectomy and an ileorectal anastomosis, there is a 10% risk of rectal cancer in 12 years.[27]

While colorectal tumors from HNPCC patients are similar to those found in sporadic colorectal cancer, there is a marked increase in the number of mucinous, signet ring cell, and poorly differentiated tumors encountered.[28] These tumors seem to incite a particular host immune response marked by an intense peritumoral lymphocytic infiltrate that is likened to that seen in the bowel wall of patients with Crohn's disease.[29]

The two genes most commonly implicated in HNPCC are *hMSH2* and *hMLH1*. In terms of overall risk of colorectal cancer, there is no significant difference in risks between these two genotypes.[30] Overall, there is about an 80% lifetime cancer risk for both groups.[31] It may be that male *hMSH2* carriers have a higher risk of colorectal cancer than females (96% vs 39%). This difference may be related to differences in risk of extracolonic cancer. The proportion of patients with colorectal cancer with rectal cancer in *hMSH2* kindreds has been shown to be in excess of the proportion of rectal cancer in *hMLH1* kindreds (28% vs 8%).[32] This risk difference may have implications for those undergoing surgery for HNPCC. In addition, the potential diagnosis of HNPCC should not be overlooked with the finding of a rectal cancer in a young patient.

There are interesting differences in the biologic behavior of the colorectal cancers for patients with HNPCC as compared to those with sporadic colorectal cancer.[33,34] It appears that HNPCC patients have an overall greater 10-year survival (69% vs 48%).[35] When compared on a stage-for-stage basis, HNPCC patients seem to do better for every stage of disease.[36] Hereditary nonpolyposis colorectal cancer tumors that penetrate the bowel wall have fewer than expected distant metastases, stage III patients have a better survival, and stage IV patients have fewer liver metastases than the general population of patients with sporadic colorectal cancer.

The better prognosis for colorectal cancer patients with HNPCC may be the result of an enhanced immune surveillance. There are tumor-infiltrating lymphocytes often noted on histology[37] in the colorectal cancers of HNPCC patients and in sporadic cases of colorectal cancer that arise as a result of MMR defects. These lymphocytes are thought to slow tumor progression through expression of interleukin-4 and tumor necrosis factor-alpha in response to human colon cancer antigen.[38]

In addition to colorectal cancer, families with the Lynch II syndrome also have familial clustering of extracolonic tumors, most commonly carcinomas of the endometrium and ovaries, transitional cell carcinomas of the ureter and renal pelvis, and cancers of the stomach, small bowel, and pancreas.[29,39,40]

Today, some believe that there is no true distinction between the Lynch I and II syndromes: Both syndromes have been linked to the

same chromosomes[41,42] in that they are only different expressions of a single syndrome.

Overall, it is colorectal cancer that characterizes these syndromes, but the extracolonic tumors cannot be ignored. In one study of 40 HNPCC families, the most common tumor was colorectal, accounting for 64%; followed by endometrial, 8%; gastric, 6%; biliary/pancreatic, 4%; and uroepithelial carcinomas, 2%.[43] Similarly studies conducted by Vasen et al.[44] and Watson and Lynch[45] also showed endometrial carcinoma to be the second most common malignancy.

The risk of breast and lung cancer in these families is unclear, with contradictory data,[45–48] probably as a result of the relatively high incidence of these tumors in the general population. Microsatellite instability (MSI) has been found in many breast cancer-affected HNPCC family members.[49]

Unfortunately HNPCC does not have a typical phenotypic expression. Unlike FAP there is no polyposis. This lack of polyposis was the first feature to differentiate HNPCC from FAP. In fact, family "G" was originally thought to have FAP, as noted in Dukes' 1947 article.[49]

The term hereditary "nonpolyposis" is somewhat misleading. Polyps do form in patients with HNPCC with an incidence similar to that seen in the general population. Mecklin et al. showed synchronous polyps are present in 19% of cases, similar to the incidence in sporadic colorectal carcinoma.[25–43] Just as in sporadic colorectal cancer, colorectal cancers in patients with HNPCC are thought to develop from adenomatous polyps. As apposed to FAP, however, they are simply not present in large numbers. As compared to sporadic polyps, the polyps in HNPCC families tend to be larger, more often right sided, more often dysplastic, and more often villous. A colonoscopic screening program found polyps in 17% of asymptomatic HNPCC family members; most of them were solitary.[50] Jass et al. reported that HNPCC adenomas were larger and had more dysplastic features.[50,52] In 31% of these polyps, they described the inclusion of mucinous components. It is thought that polyps in HNPCC patients have a more rapid growth with a shorter time of progression from adenoma to carcinoma. This justifies the short interval between colonoscopic surveillance exams for patients in HNPCC families.[51–52]

Diagnostic Criteria

The International Collaborative Group on Hereditary Non Polyposis Colorectal Cancer (ICG-HNPCC) was formed in 1989 in Jerusalem. Its goal was to develop and unify the criteria, improve patient and physician education about HNPCC, establish international collaborative groups, and promote the creation of national registries.

In 1991, the ICG-HNPCC convened a meeting in Amsterdam to define a strict set of diagnostic criteria (Table 7.2) for establishing the diagnosis of HNPCC. The criteria were termed the Amsterdam Criteria.[57]

While these criteria were helpful in standardizing diagnosis and identifying high risk individuals and families, they were primarily

Table 7.2 Amsterdam Minimum Criteria for HNPCC.

1. At least three relatives should have histologically verified colorectal cancer; one of them should be a first-degree relative to the other two; familial adenomatous polyposis should be excluded
2. At least two successive generations should be affected
3. In one of the relatives, colorectal cancer should be diagnosed before age 50

meant to be used for research purposes and increase the yield in determining the yet undefined genetics of the syndrome. Clinically, they were strict and failed to recognize any of the syndrome's extracolonic manifestations.

The Japanese Research Society for Cancer of the Colon and Rectum established clinical criteria to facilitate the inclusion of patients with incomplete family histories.[58] In 1996 the Early Detection Branch of the National Cancer Institute convened an international workshop in Bethesda, Maryland, named "The Intersection of Pathology and Genetics in the Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Syndrome." The guidelines established (Table 7.3) were designed to choose the colorectal tumors to be studied seeking MIS or RER phenotype in the attempt to identify HNPCC patients.[9] The Bethesda Guidelines are much less stringent than the Amsterdam Criteria and take into account extracolonic tumors and a number of other features found in patients and families with HNPCC.

Amsterdam Criteria II, or Revised Amsterdam Criteria (Table 7.4), were created to include carcinomas of the endometrium, small bowel, ureter, and renal pelvis. The term colorectal cancer was changed to "HNPCC-associated cancer."[59] The value of Amsterdam II Criteria has been questioned. In one study, in selecting patients for genetic test-

Table 7.3 Bethesda Guidelines for testing of colorectal tumors for MSI.

1. Individuals with cancer in families who meet the Amsterdam Criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers*
3. Individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age <45 and the adenoma diagnosed at age <40
4. Individuals with colorectal cancer or endometrial cancer diagnosed at age 45
5. Individuals with signet-ring cell-type colorectal cancer diagnosed at age <45‡
6. Individuals with a right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed at age <45†
7. Individuals with adenomas diagnosed at age <40

*Endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.

†Solid/cribriform defined as poorly differentiated or underdifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces.

‡Composed of >50% signet ring cells.

Table 7.4 Revised ICG-HNPCC criteria (Amsterdam Criteria II).

1. At least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
2. One should be a first-degree relative of the other two
3. At least two successive generations should be affected
4. At least one should be diagnosed before age 50
5. FAP should be excluded in the colorectal cancer case(s) if any
6. Tumors should be verified by pathologic examination

ing the detection rate did not differ based on use of Amsterdam I or II Criteria.[60]

Incidence

The Lynch syndrome is the most common hereditary colorectal cancer syndrome, accounting for approximately 5% of large bowel malignancies. Discovering the true incidence is difficult due to the fact that the diagnosis is based upon descriptive criteria. Most of the estimates are based on Amsterdam Criteria, which, as stated, are strict and therefore are probably below the true values.

Genetics

During the last decade molecular genetic discoveries of cancer predisposing genes have verified that a significant subset of cancers is hereditary in accord with mendelian inheritance expectations.[61] These molecular genetic findings have allowed hereditary colorectal cancer to be divided into two groups: the chromosomal instability (CIN) group and the MSI group. In the CIN pathway, mutations in tumor suppressor genes, such as *APC*, *p53*, and *DCC*, as well as proto-oncogenes, such as *Ras*, occur. These mutations are usually characterized by deletions of large regions of chromosomes that contain the tumor suppressor genes involved. The vast majority of all colon cancers, including the hereditary syndrome FAP, arise via the CIN pathway. Tumors arising from the MSI pathway demonstrate replication errors in the DNA nucleotide repeats (microsatellites) that are scattered throughout the genome, and the failure to correct such errors results from mutations in DNA MMR genes. The HNPCC colorectal cancers and approximately 15% of sporadic colorectal tumors arise via the MSI pathway.[62]

Microsatellite Instability

Microsatellite instability is the hallmark of MMR deficiency. It is the alteration in the length of a microsatellite sequence within tumor DNA when compared to normal DNA from an individual.[63] For example, CACACACACA (10 nucleotides) will become CACACACA (8 nucleotides).[64] As a result of the insertions, deletions, or mispairings, MSI arises from changes in the number of units of mono-, di-, and trinucleotide DNA repeats, which due to their repetitive nature are prone to errors during replication.[65–67] There are 50,000 to 100,000 of these

repeat sequences, the most common of which are [A]n/{T}n and {CA}n/{GT}n. They are scattered throughout the human genome and are prone to replication infidelity.[68] Because MSI can be associated with strand slippage during the replication process, they are referred to as RER+ (replication error positive) tumors as opposed to the normal RER− type. Both alleles of a mismatch repair gene must be inactive to cause a MMR deficiency. This deficiency results in errors that accumulate in the genes responsible for growth regulation that are not repaired and result in[69,70] susceptibility to tumor formation.

Microsatellite instability occurs in approximately 15% of sporadic colorectal tumors; however, MMR gene mutations have been found in only a minority of these cancers.[71,72] Most of these sporadic cancers are due to inactivation of *hMLH1* through an epigenetic mechanism. Many gene promoters contain regions containing –CG– repeats, termed CpG islands. DNA methyltransferases add methyl groups to the cytosines in CpG islands, which inhibits transcription of the gene. This hypermethylation of the CpG islands in the *hMLH1* promoter region has been found in approximately 80% of MSI-positive sporadic colorectal tumors.[73]

Discovery of Human Mismatch Repair Genes

Following the study of large kindreds using linkage analysis, the HNPCC susceptibility loci were mapped to chromosomes 2p16 and 3p21.[74,75] Expanded microsatellites were found in HNPCC, rather than regions of loss, and this was termed MSI. Microsatellite instability had already been studied extensively in bacteria and yeast, and this led to postional cloning strategies identifying the human homolog for the mutS gene on chromosome 2p (*hMSH2*, *h*uman *M*ut *S h*omolog). This was followed by the identification of the human homolog of the mutL gene on chromosome 3p (*hMLH1*, *h*uman *M*ut *L h*omologue).[76] Mutations in *hMSH2* and *hMLH1* account for the majority of reported HNPCC cases.[77] Two additional homolog mutL genes (*hPMS1* on chromosome 2q and *hPMS2* on chromosome 7q) have been cloned, mutations found in small numbers of HNPCC kindred.[78] Two other homologs of the mut S gene have also been cloned (*hMSH3* and GTBP/*hMSH6*), and mutations have been recently desribed in GTBP in HNPCC kindred.[79] These genes, and the proteins they encode for, are responsible for eukaryotic mismatch repair.

DNA Mismatch Repair Genes

hMLH1 *and* hMSH2

To date, more than 70 different germline mutations have been detected in MMR genes and shown to be associated with HNPCC. The International Collaborative Group on HNPCC has established a database of DNA mismatch repair gene mutations and polymorphisms published in 1997.[80] These data show that >80% of mutations affected the *hMLH1* and *hMSH2* genes, and that the mutations were evenly distributed with some clustering on *hMSH2* exon 12 and *hMLH1* exon 16. Most *hMSH2* mutations consisted of frame-shift (69%) or nonsense

changes (23%). Frame-shift (40%) or missense alterations (31%) mainly affected the *hMLH1*. Missense mutations appeared to produce a less severe phenotype than nonsense or frameshift mutations.

Proof that mutations in *hMLH1* and *hMSH2* are associated with MSI came from a study by Umar et al.[81] In this study a single chromosome 3 from normal fibroblasts was transfected into cells from the human colon tumor cell line HCT116, carrying a homozygous mutation in *hMLH1* and exhibiting MSI. The transfection resulted in a correction of MMR deficiency with MSI.

A recent study by Vasen et al. compared the incidence of cancer among 138 HNPCC families with *hMLH1*, *hMSH2*, and *hMSH6* mutations.[82] They found a significantly increased overall risk for developing cancer at any site in *hMSH2* mutation carriers compared with carriers of *hMLH1* mutations. The risk of developing colorectal cancer and endometrial cancer was also higher in *hMSH2* mutation carriers than in *hMLH1* mutation carriers, but the difference was not significant. An explanation for why *hMSH2* mutations are associated with a higher risk of developing cancer may involve the role *hMSH2* plays in the control of the homologous recombination of two identical DNA strands. If the DNA strands vary more than 1%, the *MSH2* protein prevents recombination.[83] Also, the *hMSH2* gene appears to be involved in pathways of transcription-coupled repair. This diversity of function may be responsible for the variation in cancer risk.

hMSH6, hPMS1, *and* hPMS2

In addition to *hMLH1* and *hMSH2*, other notable germline mutations responsible for the HNPCC syndrome include *hMSH6*, *hPMS1*, and *hPMS2*.[84,85] *hPMS1* and *hPMS2* genes have been identified as *hMLH1* analogs and are located on chromosomes 2q31–33 and 7p22, respectively.[86] It has been discovered that the mismatch binding factor consists of two distinct proteins, the 106-kDa *hMSH2* and the 160-kDa polypeptide GTBP (G/T binding protein).[87] Sequence analysis identified GTBP as a new member of the MutS homolog family, and GTBP is now called *hMSH6*. The *MSH2* protein forms two different mutS protein complexes with other MutS homologs (*MSH2/MSH6* and *MSH2/MSH3*) that recognize mispaired bases in DNA. The *MLH1* protein forms a protein complex with *PMS2* that interacts with the MutS protein complex bound to the mispaired DNA. After binding of these complexes, excision of the mispaired DNA occurs, followed by DNA resynthesis.[88] These DNA MMR genes work as a unit. Therefore, when there is a mutation in any of these genes, normal function is lost.

Effects of MMR Dysfunction

In addition to repairing errors, the MMR proteins are essential in regulating recombination events. They function as a barrier to illegitimate exchanges between quasihomologous DNA sequences. As a result, cells deficient in MMR not only have a mutator phenotype with MSI but also a hyperrecombinant phenotype with chromosomal instability.[83] They do not, however, have a massive chromosomal destabilization.

Mismatch repair mutations may be inherited or acquired as a result of exposure to environmental agents such as carcinogens like heterocylcic amines.[89] Microsatellite instability can also be seen in ulcerative colitis and chronic pancreatitis, both inflammatory diseases that may predispose to cancer. One suggested theory is that chronic inflammation can lead to saturation and subsequent failure of the MMR system, increasing the mutation rate.[90,91]

MSI Categories

Microsatellite instability phenotypes have been divided into those with high (MSI-H) and low (MSI-L) levels of instability. MSI-H is defined as instability at 30% or more of the loci studied, and MSH-L is defined as instability at 1% to 29% of loci.[92] Uncertainty exists about the clinical and biologic significance of the MSI-L phenotype because the behavior of MSL-L tumors is often similar to that of microsatellite stable (MSS) tumors.[93] There appears to be clinical and histopathologic differences between MSI-H and MSS/MSI-L colorectal cancers. Tumors with MSI-H are more likely to have mutations in genes with short repetitive tracts such as the transforming growth factor beta receptor gene, *BAX* genes, *IGF2R* gene, and others.[94–97] Compared to MSS, MSI-H cancers are less likely to have loss of *APC*[98] or mutations in K-ras[99] or *p53*.[100] MSI-H tumors are more likely to be diploid[101] and less likely to express carcinoembyronic antigen.[102] A female predilection for MSI-H tumors has been reported,[103] and MSI-H tumors are thought to have a better stage-specific prognosis.[104] MSI-H tumors are more likely to show cribiform/solid growth pattern and signet ring histology or high-grade medullary histology.[105] These tumors are also more likely to be mucinous[101] as well as exophytic.[102]

Carriers of pathogenic *hMLH1/hMSH2* germline mutations frequently show MSH-H in tumor tissue.[106] Although carriers of *hMSH6* may present with the MSH-H phenotype, they have a tendency to present with the MSI-L phenotype.[107]

MSI Status Testing

The current standard for assessing tumor DNA MMR competency is molecular MSI testing. This test involves extracting DNA from both tumor and normal tissue excised at surgery. The DNA then undergoes polymerase chain reaction (PCR) of five or more different chromosomal loci that compares microsatellites. This is achieved by running the PCR products through a gel to separate the DNA fragments by size, comparing the tumor-normal pairs, and scoring for differences between the two. Usually instability of 30% or more of the markers tested defines a tumor as MSI-H.

The results of MSI testing depend on the choice of microsatellite markers used. The National Cancer Institute workshop has recommended the use of a reference panel of two mononucleotide markers (BAT25, BAT26) and three dinucleotide markers (D5S346, D2S123, and D17S250).[92] The distinction between MSI-L and MSS tumors can only be made if a greater number of markers are utilized.[108] As mentioned

previously, MSI-H tumors have a unique pathologic phenotype, while MSH-L and MSS tumors appear to be phenotypically similar. However, the high incidence of *hMSH6d* germline mutation in suspected HNPCC families with MSI-L tumors indicates that MSI-L tumors should be accepted as evidence of MSI. It has been suggested that MSI in multiple tumors from the same family should be accepted as criteria for HNPCC.[109] However, MSI is not itself proof of HNPCC as 10% to 20% of sporadic tumors also show some degree of MSI.[110]

With modern automated technology the genotyping itself is straightforward and quick. Limitations include the facts that the testing is easiest using relatively sophisticated hardware and that both affected and unaffected tissue must be studied.[111] Because *hMLH1* and *hMSH2* account for 75% of families meeting Amsterdam Criteria, and in HNPCC patients with MSI-H tumors nearly all families are thought to carry germline mutations in *hMLH1* and *hMSH2*, Lindor et al. proposed immunohistochemical (IHC) testing of *hMLH1* and *hMSH2* in tumor samples as an alternative approach.[93] This group assessed colorectal cancers from 1,144 patients for DNA mismatch repair deficiency by two methods: MSI testing and IHC detection of *hMLH1* and *hMSH2*. IHC was found to provide a rapid, cost-effective, sensitive (92.3%), and extremely specific (100%) method for screening DNA MMR defects.

Diagnosis of HNPCC

The first clue to the presence of an inherited colorectal cancer syndrome is a family history of colorectal cancer. In general, all patients with cancer should be questioned regarding other family members with cancer. Specifically, all patients with colorectal cancer are questioned about other family members with colorectal or extracolonic tumors. The clinician is looking for evidence of a dominantly inherited colorectal cancer syndrome such as vertical transmission from one generation to another, disease at an early age, and multiple relatives affected. When affirmative responses raise suspicion that an individual is a member of an as yet undiagnosed family, a fully documented pedigree is needed. This is best undertaken by a genetic counselor or other qualified person in the context of an institutional review board-approved inherited cancer registry or inherited cancer clinic. The patient and other family members will need to sign an informed consent, and diagnoses will need to be confirmed with patient records, pathology reports, or death certificates.

If the Amsterdam Criteria are met, the patient and at-risk family members may be offered genetic testing. The use of these criteria as an indication for germline MMR gene testing results in detection of a mutation in 40% to 60% of families. The use of less strict criteria is associated with significantly lower yields.[112] These criteria are strict and fail to account for small family size and/or presence of extracolonic tumors. At this time, however, there is insufficient data to justify routine MMR gene testing unless these criteria are met.

The Bethesda Guidelines suggest that when the suspicion of HNPCC is raised and tumor tissue is available, testing for MSI as evidence of MMR deficiency should be considered. Microsatellite instability is an imperfect but helpful molecular "fingerprint" of HNPCC. It can be helpful in guiding choices about whether further genetic testing will be informative. The presence of a microsatellite-unstable tumor in the setting of a strong family history is highly suggestive of HNPCC. A microsatellite-stable tumor in a young patient is unlikely to represent HNPCC. Almost all tumors arising within the context of HNPCC are microsatellite unstable. Microsatellite instability is present in approximately 15% of sporadic colorectal cancers. Therefore, with an MSI-positive tumor from an affected family member the diagnosis of HNPCC must be confirmed by MMR gene testing.

Commercially available testing is currently available for mutations in *hMLH1* and *hMSH2.* Because screening in general starts after the age of 20, genetic testing is not offered until the age of 18 to 20 or 10 years younger than the youngest affected family member. A positive test confirms the diagnosis, and all first-degree relatives are considered to be at 50% risk of carrying the mutation. Genetic testing in these family members should give conclusive results. Affected family members are considered at high risk of colorectal and extracolonic malignancy, and appropriate screening recommendations are made. In a family with a known mutation, a negative test result indicates that the family member, and his or her children, is not at risk for HNPCC, and screening for colorectal cancer is no different than that for the average risk patient.

For individuals who meet criteria for genetic testing in which there is a "no mutation detected" result obtained, the patient and all first degree relatives should continue with recommended HNPCC screening.[113]

Screening for HNPCC

Colorectal Neoplasms

Provisional screening recommendations have been developed for individuals with MMR mutations.[114,115] These recommendations may also apply to nontested individuals from MMR mutation positive HNPCC families and those from families with an autosomal dominant predisposition to colorectal cancer. Full colonoscopy to the cecum with removal of adenomatous polyps is recommended beginning at age 20 to 25 or 5 years earlier than the age of cancer diagnosis in the youngest affected relative.[116,117] Examinations are performed every 1 to 2 years for the duration of the patient's life. No randomized controlled trials have been performed to substantiate the benefit of colonoscopy in MMR gene mutation carriers. However, colonoscopic polypectomy of adenomas has been shown to significantly reduce the incidence of colorectal cancers in nontested at-risk individuals of HNPCC kindreds.[118] Using experimental decision analysis models evaluating cancer pre-

vention strategies in 25-year-old MMR mutation carriers, colonoscopic screening increased life expectancy by 7 to 13.5 years.[119]

Extracolonic Neoplasms

Endometrial cancer is the second most common cancer seen in HNPCC families, with a cumulative risk of 30% to 60% in MMR mutation carriers.[120,121] Annual screening for endometrial cancer is recommended beginning at age 25 to 35 and continued throughout the patient's life.[122] Screening options include endometrial aspirate and transvaginal ultrasound. Such methods are accepted screening tools for postmenopausal women but have not yet been tested in younger asymptomatic patients.[116]

Insufficient data exist to make recommendations for the other HNPCC-related neoplasms, including stomach, small-bowel, biliary tract, urinary tract, and ovarian tumors. However, screening for a specific cancer is recommended if this tumor is diagnosed in a family member. The age for beginning screening is based on the individual family cancer history. Upper gastrointestinal endoscopy is the screening method used most often for stomach cancer. Urinalysis and abdominopelvic ultrasound are used to screen for cancer of the urinary tract. Serum CA125 and transvaginal ultrasound are the screening tools for ovarian cancer.

Management of HNPCC

Hereditary nonpolyposis colorectal cancer is characterized by early-onset colorectal cancer with right sided predominance, synchronous or metachronous neoplasms, and extracolonic neoplasms including endometrial, transitional cell carcinoma of the renal pelvis and ureters, and small-bowel adenocarcinoma. The management can be divided into the following categories: management of an affected individual with untreated colorectal cancer, management of an affected individual with colorectal cancer treated with less than an abdominal colectomy, management of the yet unaffected individual with a germline MMR mutation, and the management of individuals who developed adenomas but not carcinoma.[123]

Affected Individual with Untreated Colorectal Cancer

The treatment for a newly diagnosed HNPCC individual with a colon carcinoma is an abdominal colectomy with ileorectal anastomosis. Prevention of metachronous colon cancer is the rationale for total colectomy at the time of the initial cancer surgery. The risk of metachronous colorectal cancers is estimated to be as high as 40% at 10 years after less than an abdominal colectomy.[124] This risk may be up to 72% at 40 years after the diagnosis of a colorectal cancer.[125] Colectomy with ileorectal anastomosis, however, will not eliminate the risk of colorectal cancer in HNPCC patients. The incidence of colorectal cancer after this procedure has been reported from 6% to 20%.[126,127] Abdominal colectomy with ileorectal anastomosis was originally de-

scribed by Mayo and Wakefield in 1936.[128] This procedure involves removing the entire abdominal colon and performing an anastomosis in the true rectum.[129] This is not an innocuous procedure, and because of the potential morbidity, it is usually not ideal for patients whose procedure is palliative or in those with resectable metastatic disease.[123] These patients may be better served with a segmental resection and surveillance.

The presentation of a female with colorectal cancer raises the issue of whether a prophylactic total abdominal hysterectomy and bilateral salpingo-ophorectomy (TAH-BSO) should be performed synchronously with the colectomy. Endometrial cancer is the most common extracolonic tumor in HNPCC, with the incidence in putative gene carriers being reported as 30% by age 70.[130] Dunlop et al. reported a 42% risk of developing endometrial cancer vs a 30% risk of developing colorectal cancer in HNPCC patients.[131] As a result, for patients who are postmenopausal or have completed their families, consideration should be given to a prophylactic TAH-BSO, although there is no data to support this recommendation.

For HNPCC patients presenting with rectal carcinoma, efforts should be made for sphincter preservation. The preferred surgical procedures for patients with HNPCC presenting with rectal cancer are total proctocolectomy with ileal pouch–anal anastomosis. If the features of the tumor do not allow for sphincter preservation, an end ileostomy will follow the proctocolectomy.[123] Moslein et al. reported that 54% of HNPCC patients presenting with rectal cancer developed a metachronous colonic cancer at a mean of 7.4 years.[132] Segmental resections such as low anterior resection and abdominoperineal resection are not the preferred operative approaches. However, stage of the disease and patient factors will impact the final decision for type of operation.

Affected Individual Treated with Less than Abdominal Colectomy

Patients with HNPCC treated with less than an abdominal colectomy should undergo surveillance colonoscopy every 1 to 2 years. The efficacy of extracolonic cancer screening recommendations remains to be proven.[133]

Unaffected Individual with Germline MMR

Prophylactic abdominal colectomy is a controversial option for carriers of MMR gene mutations with normal colons. The penetrance in HNPCC is 80% to 85%, meaning that 15% to 20% of such individuals will not develop colorectal cancer in their lifetime.[134] The benefits of prophylactic surgery include eliminating the majority of the colon at risk for cancer and eliminating surveillance colonoscopic examinations and the accompanying complications.[123] Against prophylactic colectomy is the fact that patients will still have rectal mucosa at risk requiring surveillance examinations as well as cancer risk in other extracolonic organs. Because the organ in which the first carcinoma arises is not predictable, theoretically there may be no end of prophylactic surgery in these patients.[135]

Mathematical models used to derive survival benefits of prophylactic surgery in gene carriers show no advantage of more than 24 months as opposed to endoscopic surveillance assuming 100% compliance.[135,136] Jarvinen et al. reported a 62% decrease in colorectal cancer incidence and 65% decrease in overall death rate in HNPCC at-risk individuals who underwent surveillance with flexible sigmoidoscopy and barium enema or colonoscopy every 3 years over a 15-year period compared to those HNPCC at-risk individuals who refused surveillance.[137] From this study, it appears that colonoscopy every 2 to 3 years is an effective management option for patients with a germline MMR gene mutation who have not yet developed colorectal cancer. There currently is no evidence for or against prophylactic colectomy in such patients. One possible situation where prophylactic colectomy could be performed is the patient where colonic surveillance is technically not possible or a patient who refuses colonoscopic surveillance. Patients who undergo colectomy should be told that they will require lifelong endoscopic evaluation of their rectal segment. Patients also need to understand that the alternative to colectomy is lifelong colonoscopic surveillance.[138]

Individual with Adenoma but Not Carcinoma

Colonic adenomas in patients with HNPCC are thought to be larger, more advanced histologically, and more dysplastic than adenomas in the general population. This observation suggests that the adenoma carcinoma sequence is hastened[139] in HNPCC. Taking this information into account, prophylactic abdominal colectomy could be considered a reasonable treatment option, especially if adenomas are numerous or frequently recur after endoscopic removal. In some patients with HNPCC, colonic neoplasms present as plaque-like, flat lesions that can be difficult to identify and as a result may be difficult to endoscopically remove.

Endometrial Cancer

Abdominal hysterectomy and bilateral salpingo-oophorectomy is standard operative management for endometrial cancer, but there is insufficient evidence to recommend for or against prophylactic hysterectomy as a measure for reducing cancer risk.[140] There are no data on the efficacy of TAH-BSO in HNPCC, although it is an option for prevention of endometrial and ovarian cancer in women known to have HNPCC or to be carriers of HNPCC-associated mutations.[141]

Chemoprevention

Population-based studies have suggested a role for aspirin in lowering the rate of adenoma development and carcinoma.[142] Sulindac reduces the rate of adenoma development in FAP.[143] Neither agent has been studied for use in HNPCC, and clinical evidence is needed before these therapies can be recommended.

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8

Hereditary Ovarian Cancer and Other Gynecologic Malignancies

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Advances in molecular biology have resulted in an explosion of knowledge regarding the physiological pathways of development of inherited gynecologic malignancies. As a result, investigators are beginning to understand the sequence of genetic alterations that lead to the malignant phenotype. This knowledge allows for the identification of individuals carrying genetic alterations that can be considered at high risk for the development of gynecologic cancer. In addition, increased knowledge of the molecular changes that occur during the process of carcinogenesis allows for opportunities to intervene and potentially reverse or prevent the progression of cells to the malignant phenotype.

This chapter, therefore, will provide the practitioner with an overview of genetic alterations that occur in families with a predisposition primarily to ovarian cancer and the methods of risk assessment in these patients. Moreover, available methods of screening and strategies of prevention will be reviewed. With this information, it is anticipated that the practitioner will be well equipped to effectively manage these interesting patients.

Ovarian Cancer

Genetic Abnormalities in High-Risk Individuals

The concept that individuals within certain families were predisposed to the development of epithelial ovarian cancer has long been recognized. A report from 1969, in *Lancet*, details a family where four sequential generations of women were diagnosed with ovarian cancer.[1] Through the 1980s and 1990s larger familial cohorts were identified where high penetrance of ovarian cancer was observed. This led to the classification of three specific syndromes: site specific, breast/ovarian cancer syndrome, and Lynch syndromes.[2]

It is not until recently, with the advent of modern molecular biology techniques, that associated genetic mutations have been identified. Groundbreaking work by Easton et al. resulted in the identification of a genetic link of ovarian cancer to mutations in the *BRCA1* gene.[3] Ini-

tial publications linking *BRCA1* and *BRCA2* to elevated risk of ovarian cancer suggested a lifetime risk of ovarian cancer of 63% by age 70, where the normal population risk approximates 1%.[3] Moreover, Beller et al. demonstrated the high frequency of ovarian cancer and associated *BRCA* mutations in women of Ashkenazi Jewish descent, strengthening the idea that the elevated risk of ovarian cancer is an inherited phenomenon.[4] Subsequent population-based studies have expanded the population of patients with associated *BRCA1* and *BRCA2* mutations, and the estimated lifetime risk of ovarian cancer in these populations has been reduced. Based on accumulated studies, that lifetime risk of ovarian cancer in individuals with mutations in the *BRCA1/BRCA2* genes is between 15% and 30%.[5,6] Additional studies have suggested that mutations in the *BRCA2* gene are associated with markedly lower risks of ovarian cancer, in contrast to the persistent high susceptibility observed in risk of breast cancer.[7]

Multiple genetic etiologies of cancer can and do exist, so that not all inherited forms of epithelial ovarian cancer are attributable to *BCRA1* and *BRCA2* mutations. Indeed, Stratton et al. suggested that *BRCA1* mutations occur in only 5% of sporadic ovarian cancer observed in patients less than age 70.[8] These "other" genetic mutations encompass alterations in both known and unknown ovarian cancer associated genes. This concept is important in counseling patients regarding inherited risk. When a defined *BRCA* mutation is present in a pedigree affected by multiple cases of breast and ovarian cancer, then a positive or negative genetic test can be useful in clinical decision making. However, if the BRCA gene is normal throughout multiple affected relatives, then the contributed risk may be due to other inheritable genetic alterations, and *BRCA* testing is less helpful.

Population-based studies have demonstrated a wide range of variation regarding the prevalence of *BRCA* mutations where a pedigree is suggestive of elevated risk. Multiple studies of patients with family histories suggestive of an increased familial risk of ovarian cancer have demonstrated the *BRCA* gene to be mutated in 0% to 50% of patients.[9–11] Sutcliffe et al., using the UKCCCR Cancer registry, retrospectively identified patients having two or more first-degree relatives having ovarian cancer.[12] In this patient cohort, a relative risk of developing ovarian cancer remained elevated at 11-59% when no abnormality in *BRCA1* was noted. A recent Gynecologic Oncology Group (GOG) study prospectively identified ovarian cancer patients with significant family histories of breast and ovarian cancer.[11] Of 26 eligible patients screened for mutations, 46% (12) had abnormalities in the *BRCA* genes (*BRCA1*-8 mutations, *BRCA2*-4 mutations). An increasing frequency of these mutations was observed as the number of affected relatives increased.

While population-based studies have established linkage between mutations in the *BRCA1* gene and risk of ovarian cancer, laboratory studies have suggested an actual role for the *BRCA* gene as a tumor suppressor. The protein product of the *BRCA1* gene appears to interact in a pathway that repairs damaged DNA.[13] Transcriptional regulation of the *p53* and *p21* promoters and alteration of Rad51 protein appear to be influenced by the *BRCA* protein product.[14,15]

Hereditary nonpolyposis colorectal cancer (HNPCC) is another genetic syndrome where an elevated risk of ovarian cancer is observed. Hereditary nonpolyposis colorectal cancer is associated with mutations in the *MSH2* or *MLH1* genes thought to result in defects of DNA mismatch repair, leading to microsatellite instability.[16] Cohort studies have documented an increased risk of ovarian cancer slightly greater than 10% by age 70 in female patients afflicted by this syndrome.[17]

While most ovarian cancers where elevated inherited risk is observed are of epithelial derivation, rare ovarian tumor types have been observed in association with uncommon genetic syndromes. Ollier's disease has been associated with the development of juvenile granulosa cell tumors.[18] Approximately one third of patients diagnosed with ovarian sex cord tumor with annular tubules have Peutz-Jeghers syndrome.[19] Gorlin's syndrome is associated with an inherited predisposition to develop benign ovarian fibromas.[20] Ataxia telangiectasia (AT) is an autosomal-recessive disorder with a gene abnormality identified on chromosome 11q. A few patients with AT have been reported to develop ovarian dysgerminoma.[21] Gonadoblastoma, which refers to a tumor exhibiting both germ cell and sex cord stromal elements, have been known to develop in patients where a Y chromosome is present but a female phenotype exists.[22]

Assessment of Individuals at Elevated Inherited Risk of Ovarian Cancer

The evaluation of who might be considered at elevated risk for ovarian cancer should be initiated in the context of a careful pedigree analysis. Special emphasis should be placed within the pedigree analysis on multiplicity of breast and ovarian cancer within a familial cohort, as well as young age of onset.

Emphasizing multiple cases of cancer and young age at onset, the American Society of Clinical Oncology (ASCO) has set forth guidelines regarding testing for genetic mutations.[23] The ASCO criteria for considering genetic testing include families with (1) greater than two breast cancers and greater than one ovarian cancer at any age, (2) greater than three breast cancers before age 30, (3) sister pair with two breast cancer and two ovarian cancers, or one of each before age 50, and (4) breast cancer before age 30. Again, one should bear in mind that genetic testing encompasses relatively few genes known to place individuals at risk. Situations may, therefore, arise where family history alone is sufficient for considering a screening or preventive intervention.

While guidelines, such as these, can help suggest the patient at risk, the decision to perform a genetic test is multifaceted and is best determined under the auspices of a comprehensive multidisciplinary genetic counseling program. Consideration should be given to how the information will be utilized by the patient and provider. One should consider who will be the recipient of results and how the information will be dispersed throughout a family cohort. One should bear in mind that the most useful individual to test is an affected relative, as a test indicating a mutation for *BRCA1/BRCA2* will be more informative than

a negative test. Finally, a negative test in affected individuals is problematic as other "unknown" genes may be operative in individual family cohorts. As such, it remains reasonable to consider interventions based on strong family history alone.

Screening Interventions in High-Risk Individuals

Recognizing that therapeutic intervention of any advanced-stage solid tumor is unlikely to produce a substantial cure rate, attention has been given to screening to identify early-stage disease amenable to curative resection. The fundamental challenge in this strategy centers upon the relatively low prevalence of this disease. As such, the effectiveness of any screening strategy will be severely hindered by a low-positive predictive value. Given an estimated prevalence of 50 cases per 100,000 population, a test with 99% specificity and 100% sensitivity would yield only 1 in 21 women undergoing surgical intervention with ovarian cancer.[24] The screening trials performed to date in average risk women would support these problematic statistics. A representative study by Jacobs et al. utilized screening with CA125 and ultrasound in 22,000 subjects.[25] These authors identified 41 women with positive screening results, of whom 11 were noted to have cancer. It is important to note that 70% of the screening-identified cancers were stage III or IV.[25]

Both the UK trial by Jacobs et al. and a Swedish CA125 screening trial provided substantial numbers of patients with longitudinal CA125 values.[26] As investigated by Skates et al., graphical analysis of data suggested that information that differentiates ovarian cancer cases prior to clinical symptoms from all other women is contained in the pattern of CA125 over time.[27] In women subsequently diagnosed with ovarian cancer, CA125 values rose exponentially over time, whereas in most other women CA125 values remained relatively stable over time even when initially elevated. This information is in addition to the traditional interpretation of the CA125 value, namely, whether it exceeds a given cutoff value of 30 or 35 U/mL. From statistical models of the longitudinal CA125 behavior in cases and controls, Skates et al. developed a method for calculating the probability of having ovarian cancer given the subject's CA125 values and age. This "risk of ovarian cancer algorithm" (ROCA) efficiently identifies women at higher risk for more aggressive interventions. Analysis of the UK and Swedish data demonstrates the power of ROCA, with a vast increase in the positive predictive value (PPV) from 2% to 16% achieved simply by using longitudinal information rather than a fixed cutpoint across all subjects.[27] This increase in PPV is obtained while maintaining a high level of sensitivity of over 80%. This ROCA forms the basis for a large multicenter screening trial in women at increased risk of ovarian cancer currently being conducted in the United States.

As a result of the lack of specificity of using CA125 as a screening marker, alternative strategies are being developed. An arbirtrary goal of a PPV for early-stage disease has been suggested to be 10%. This would imply that 10 interventions would be performed for each case of early-stage cancer identified. Van Nagell et al. have approximated a

10% PPV utilizing an ultrasound screening protocol.[28] These authors performed screening ultrasounds on 14,469 "normal risk" subjects. Seventeen cancers were identified, of which 11 were stage I. This yielded a PPV of 9.4%. A criticism of this study, however, was that 6 of 11 of the stage I tumors were of a granulosa cell/stromal histology or ovarian tumors of low malignant potential. This finding was also observed in an ultrasound study by Sato et al. involving 51,550 subjects.[29] Twenty-four tumors were identified, of which 17 were stage 1; however, 5 of the 17 were granulosa cell tumors or tumors of low malignant potential. These tumor types have a markedly more indolent course, and the metastatic behavior of these tumors is in direct apposition to the typical epithelial cell ovarian tumor for which screening programs are being designed. However, given these preliminary studies, further trials are indicated using ultrasound as a screening modality in high-risk individuals where the prevalence of disease would be higher, potentially enhancing the PPV for epithelial early-stage ovarian cancer.

Preliminary data utilizing serum proteomics is currently being evaluated for potential clinical utility. Petricoin et al. recently reported on a proteomic approach to screening serum samples for protein expression patterns that might suggest ovarian cancer. The sensitivity of 100% and specificity of 95% is promising for use in high-risk women. But, these test characteristics would lead to a PPV that is too low for use in the general low-prevalence population.[30] These exciting findings will need to be verified in large scale clinical trials in high-risk women before their utility is better defined.

Prevention of Ovarian Cancer in High-Risk Populations

Strategies that focus on prevention may provide a rational approach for meaningful reductions in deaths attributable to ovarian carcinoma. Increasing knowledge of inheritable genetic lesions in cohorts of patients allows for the identification of high-risk populations. Moreover, while the molecular events leading to the development of ovarian cancer are unknown, a carcinogenic pathway can be conceptualized that involves uninterrupted ovulation in a growth-stimulating hormonal milieu leading to increased probability of genetic lesions and expansion of tumorigenic clones.[31]

Oral contraceptives (OCs) have been suggested as potential preventive agents that may reduce the subsequent risk of ovarian carcinoma.[32–50] Historically, the effect has been attributed to reduction in the number of ovulatory events associated with regular use of OCs. More recent data, however, suggest that the protective effect of OCs may be more complex. An innovative study that supports the use of progestins as chemopreventive agents in ovarian carcinoma was recently published by Rodriguez et al. In a randomized design, these authors examined the effect on ovarian epithelium of levonorgestrel in 130 ovulatory macaque monkeys.[32] This progestin was administered over a period of 35 months, at the end of which the animals were sacrificed and their ovarian epithelium were examined for apoptosis using immunohistochemical techniques.

These authors demonstrated significantly increased apoptotic cell counts in the ovarian epithelium of animals exposed to progesterone and hypothesized that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCs.[32] This idea is a departure from the widely accepted theory that suppression of incessant ovulation is responsible for reduced risk of ovarian cancer. Moreover, they theorized that oral contraceptive progestins may decrease the risk of ovarian cancer by increasing the tendency of ovarian epithelial cells that have incurred genetic damage but are not yet neoplastic to undergo apoptotic death.[32]

Several studies have suggested that the degree of protection is associated with the duration of use of OCs.[38,40,41,51–53] The length of protection appears to be strongly correlated with duration of use. Prolonged risk reduction has been reported when OCs are used longer than 4 to 6 years, and minimal benefit has been observed if utilization is restricted to 6 months to 2 years.[38,40,52,53] Moreover, the protective benefit of OCs diminishes with time and returns to baseline approximately 15 years after the last regular use of OCs.[38,40,41]

The influence of the estrogen/progestin content of a particular OC on subsequent ovarian cancer risk is an issue needing further study. Ness et al. demonstrated identical risk reduction for OCs with high-estrogen/high-progesterone content when compared with low-estrogen/low-progesterone content pills.[54] However, a recent observational study by Schildkraut et al. suggested that low-progesterone OC formulations were associated with a significantly higher risk of ovarian cancer when compared with high-progesterone potency OC formulations.[55]

One of the strongest risk factors for the subsequent development of ovarian cancer is a history of multiple affected family members. Studies by Gross et al. and Tavani et al. demonstrated a risk reduction with OC use in women with strong family histories.[56,57] These results led Tavani et al. to suggest that 5 years of OC use in "high-risk women" can reduce ovarian cancer risk to the level observed in studies of low-risk women and in high-risk women who never used OCs but have parity as a protective factor.[57] Further study is needed, however, in actual *BRCA1* or *BRCA2* gene mutation carriers, mutations with high risk of ovarian cancer. While an initial study by Narod of 207 women with confirmed *BRCA1/BRCA2* mutations demonstrated a statistically significant risk reduction with OC use,[35] this finding was not confirmed in a subsequent study of 244 women by Modan et al., where a risk reduction was present but not statistically significant.[58] Thus, further studies of the association between OCs and ovarian cancer in women with *BRCA1* and *BRCA2* mutations are necessary to clarify this issue. The protective effect of OCs would appear to be consistent across races as John et al. demonstrated a reduction in risk of 0.6 in African-American women with OC use of 6 years or more.[39]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have generated significant enthusiasm as chemopreventive agents, in particular for colon carcinoma.[59] While some observational studies suggest a reduction of ovarian carcinoma risk with the use of some NSAID deriva-

tives, the rationale for their use as chemopreventive agents has been lacking. However, recent animal studies examining the effects of NSAIDs on normal ovulation shed light on the potential mechanisms. Foremost, several classes of NSAIDs have been demonstrated to inhibit ovulation across multiple species of vertebrates.[60] Indomethacin appears to inhibit ovulation in a dose-dependent fashion.[61,62] In vitro analysis has suggested that inhibition of COX-2 leads to downregulation of local prostaglandins that may result in interactions with downstream mediators of surface epithelial cell apoptosis inhibiting rupture of the epithelial lining of the dominant follicle.[61] Nonsteroidal anti-inflammatory drugs have also been demonstrated to result in potent growth inhibition and increased apoptosis in ovarian cancer cell lines.[63]

Interesting evidence for an antigonadotropic effect in animals also exists for acetaminophen. Acetaminophen has a phenol ring, similar to estradiol, and an acetyl group similar to progesterone, indicating a potential sex steroid-antagonist property.[64,65] Evidence of this antigonadotropic property was suggested by toxicology studies demonstrating uterine, ovarian, and testicular atrophy in rats fed acetaminophen at 25,000 ppm.[65] In this study, the frequency of ovarian cysts was 23% in mice exposed to 3,000 to 6,000 ppm acetaminophen compared with 38% of mice either not exposed or minimally exposed.[65]

Several observational studies of the association of analgesic use and risk of ovarian cancer have yielded inconclusive results. Compared with women who used aspirin rarely or not at all, Cramer et al. demonstrated a 25% reduction in risk among women with at least weekly use of aspirin over a 6-month period, while Tavani et al. demonstrated a 28% lower risk in "former users" of aspirin.[64,66] One should interpret these results with caution, however, as neither were statistically significant, and a study by Moysich et al. demonstrated no evidence of reduced risk in aspirin users.[67] Epidemiological evidence also exists for acetaminophen's chemopreventive activity. Cramer et al. found that ovarian cancer risk among daily acetaminophen users was 61% lower than among nonusers.[64] Similarly, Moysich et al. observed a 44% reduction in risk with regular acetominophen use, defined as use at least once a week.[67] In both studies, the protective effect of acetaminophen was statistically significant. Rodriguez et al. also reported a 45% lower death rate from ovarian cancer in women using acetaminophen daily; however, this finding was not statistically significant. In this particular study, only 5% or 5,731 women (of 11,482 total women reporting any acetaminophen use) reporting daily acetaminophen use, and this small number of subjects could have contributed to a wider confidence interval.[68] A case control study reported by Rosenberg et al. examining the potential protective benefit of regular acetaminophen use found little evidence of an ovarian cancer risk reduction associated with this analgesic.[69] However, together, current data presents a rational argument for the continued study of these agents in clinical and preclinical investigations.

An agent used for chemoprevention should have the capacity to cause cellular differentiation or lead to apoptosis in an initiated cell destined to become malignant. Experimental evidence indicates that

retinoid derivatives can inhibit growth and promote cellular differentiation in ovarian cancer cells. In vitro experiments have demonstrated growth inhibition after application of all-trans retinoic acid to CAOV3 ovarian carcinoma cells.[70] In addition, Caliaro et al. and Brooks et al. demonstrated increased induction of cytokeratins in cultures of ovarian cancer cells exposed to retinoic acid, suggesting a role in the differentiation of these cells.[71,72] Finally, Supino et al. exposed A2780 ovarian cancer cell cultures to fenretinide and observed an increase in apoptosis.[73] The ability of retinoid derivatives to prevent ovarian carcinoma is also suggested in an interventional study in humans by Veronesi and De Palo.[74,75] These authors reported a phase III trial of fenretinide for the prevention of second breast cancers. Subgroup analysis demonstrated a significantly lower incidence of development of ovarian cancer in the treatment group. These results, however, must be interpreted with caution due to the limited number of ovarian cancer cases and the statistical pitfalls inherent in subgroup analyses. These studies have helped define the basis for an ongoing clinical trial (GOG190) examining the tissue effects of preoperative fenretinide administration over 4 to 6 months in women undergoing prophylactic oophorectomy due to high familial risk of ovarian cancer.

Surgical Strategies to Reduce the Risk of Ovarian Cancer

The ability to define populations of women at increased inherited risk for ovarian cancer has made consideration of prophylactic bilateral oophorectomy (BSO) in these cohorts a rational consideration. Recent studies defining lifetime risk for ovarian cancer in women with *BRCA1* mutations would suggest a cumulative risk of 15% to 30%.[76] In addition, increased risk of ovarian cancer is present with mismatch repair gene defects observed in the Lynch type II syndrome.[77] Vasen et al. suggested an eightfold elevation in risk of ovarian cancer in women with HNPCC.[78] While it is tempting to recommend OCs or prophylactic surgical procedures to these patients, further study is needed in the context of this syndrome before recommendations for these preventive measures can be made.

A decision analysis has been performed to assess the effectiveness of prophylactic oophorectomy in women with *BRCA1* mutations. Schrag et al. constructed two hypothetical populations of women: one consisting of women age 30 and the other consisting of women age 60, both with *BRCA1* mutations and undergoing oophorectomy.[76] A potential benefit of up to 1.7 years of life gained was observed in the modeled cohort of women age 30. In addition, it appeared that any benefit was minimal in women of age 60, and a delay of BSO of up to 10 years in the 30-year-old cohort did not decrease life expectancy. When considering the risk of the procedure, a risk level appreciably lower than the risk of disease would be desirable. A study by Eltabbakh et al. examined 62 women undergoing BSO due to family history.[79] Two operative complications were noted (intraoperative vascular complication, postoperative bleeding), and no deaths were reported. Therefore, in patients with elevated inherited risk of ovarian carcinoma, it

seems reasonable to consider prophylactic oophorectomy after childbearing is completed. Patients should also be aware of theoretical concerns regarding the survival benefit of undergoing prophylactic oophorectomy after age 60.[76]

Patients undergoing prophylactic oophorectomy must be counseled that the reduction in risk of ovarian-type cancers is not absolute. Piver et al., in reviewing the Gilda Radner Familial Ovarian Cancer Registry, identified 324 women who had undergone prophylactic BSO.[80] These authors identified six women (2%) who developed ovarian-type cancer, either from a remnant segment of ovarian tissue or carcinoma of the peritoneal "field" 27 years after surgery.

A substantial number of women undergoing prophylactic oophorectomy will have an occult cancer of the ovaries identified on histological review. In the combined series of Salazar and Deligdisch, 3 of 51 patients undergoing prophylactic oophorectomy were found to have occult early ovarian cancers.[81,82] In addition, a recent series published by Scheuer et al. identified two early-stage cancers of the ovary and fallopian tube, respectively, in 90 women undergoing prophylactic oophorectomy.[83] In addition, these authors reported the detection of three additional cases of early-stage cancer on preoperative screening in these high-risk individuals. A larger series is needed to confirm the true risk of occult cancer, however, as no early ovarian carcinomas were identified by Barakat et al. in 18 patients undergoing prophylactic oophorectomy.[84] This finding underscores the need for adequate communication with the pathologist and surgeon, as well as careful histological examination using multiple sections of these ovarian specimens.

More recently, two prospective investigations confirmed the effectiveness of risk reducing surgery in patients carrying *BRCA* gene mutations. In the report by Kauff et al., 1 case of ovarian cancer was subsequently diagnosed in 98 women undergoing BSO when compared to 4 ovarian cancers identified in 72 women not undergoing surgery after a median follow-up of 2 years.[85] A significant reduction in the hazard ratio for development of breast cancer was also observed. Similarly, Rebbeck et al. also observed a protective benefit for subsequent development of both breast and ovarian cancer in *BRCA* mutation-positive individuals undergoing risk reducing bilateral salpingo-oophorectomy.[86] These authors compared 259 women undergoing BSO with 292 matched controls. Six women (2.3%) were diagnosed with stage I ovarian cancer at the time of surgery. After a mean follow-up of 8.8 years, prophylactic oophorectomy significantly reduced to risk of development of ovarian cancer in these high-risk individuals (hazard ratio 0.04; 95% confidence interval 0.01 to 0.16). This important study offers the strongest evidence, to date, of the potential benefit of risk-reducing prophylactic oophorectomy in high-risk individuals.

While not recommended as a sole procedure for prophylaxis against the development of ovarian cancer, retrospective reviews of women have noted decreased risk of developing ovarian cancer among women who had undergone tubal ligation.[33,87–92] This interesting finding suggests that limiting exposure of the ovary to environmental carcinogens can prevent the development of ovarian cancer. The ability of tubal lig-

ation to reduce the risk of ovarian cancer appears to be operative in individuals with *BRCA1* or *BRCA2* mutations. Narod et al. compared 232 *BRCA*-positive women with a history of ovarian cancer to 232 *BRCA*-positive control women.[89] A history of tubal ligation was associated with a statistically significant reduction in risk by 63%. Depite the protective effect of tubal ligation, it would seem prudent to remove the adjacent ovaries if laparoscopic surgery is contemplated in women at elevated risk due to genetic testing or strong family history of ovarian carcinoma.

Other Gynecologic Malignancies Associated with Inherited Risk

Endometrial Carcinoma

Although endometrial carcinoma is the most common gynecologic malignancy in the general population, it typically is not observed to be associated with elevated inherited risk in and of itself. However, in women who inherit HNPCC-associated germline mutations, an increased risk of endometrial cancer is observed. Endometrial cancer is the second most common cancer identified in HNPCC individuals following colon cancer.[93] It is estimated that women with HNPCC-associated gene mutations (mutations of the *MLH1* and *MSH2* genes) harbor a risk of endometrial cancer of 60% by age 70 compared with 2% in the general population.[93]

The *MLH* and *MSH2* gene complexes are thought to play a role in mismatch repair.[94] When these genes are defective, increased microsatellite instability is observed and thought to be a precursor lesion to the cancer cell phenotype.[94] Microsatellite instability has been observed in endometrial carcinomas.

In managing the patient with HNPCC-associated mutations, the practitioner should include in the evaluation annual transvaginal ultrasound and endometrial biopsy beginning around the age of 30.[95] In addition, if subtotal colectomy is considered in the management of an individual patient, consideration can be given to performing hysterectomy with or without salpingo-oophorectomy at that time.[95]

Cervical Carcinomas

Gynecologic malignancies with increased inherited risk are exceedingly rare outside of the scope of ovarian and endometrial cancer. Peutz-Jehgers syndrome is an autosomal dominant syndrome where individuals are prone to the development of intestinal polyps and subsequent malignancy of the gastrointestinal tract and pancreas. In addition to the association with ovarian sex cord stromal tumors with annular tubules as mentioned previously, women affected with this syndrome are also at increased risk for adenoma malignum or minimal deviation adenocarcinoma (MDC) of the cervix.[96,97]

Histologically, MDC is characterized by cytologically bland glands that penetrate the cervical stroma to a depth not typically encountered.

Due to the deep involvement of the glands a cone biopsy is often indicated in the diagnostic management of this disorder. When diagnosed, the treatment of MDC is radical hysterectomy, while radiation therapy is preferred in more advanced stage disease.

Conclusions

Tremendous progress will be made in the near future through advances in molecular biology and genetic testing. Further insights into genes that contribute to enhanced risk of gynecologic malignancies will be identified. This field, while exciting, is young, and a careful approach is encouraged in recommending interventions to this group of patients at high risk for ovarian cancer and other gynecologic malignancies. We would also encourage participation in well-designed clinical trials so that the true benefit of interventions can be determined. It is hoped through the careful analysis of risks and potential benefits of risk identification and intervention, the management of this group of patients will rapidly improve.

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9

Genetic Aspects of Urologic Malignancies

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Cancers of the urologic tract and male genital system account for approximately 22.4% of all malignancies in the United States.[1] Similar to other organ systems, familial predispositions to urologic malignancies have been well recognized for centuries. Through genetic studies of families with such predispositions and slow but steady progress characterizing the function of individual genes, as with other tumor types, the molecular basis for several urologic cancers is now becoming apparent. In this chapter, the current state of understanding concerning genetic predisposition and somatic mutations underlying prostate cancer, bladder cancer, Wilms' tumor, renal cell carcinoma, and testicular cancer will be reviewed. The clinical significance regarding screening, diagnosis, and implications for therapeutic management clearly remains in its infancy at this time, as our understanding of these malignancies grows and the availability of genetic testing rapidly increases.

Prostate Cancer

Incidence

Prostate cancer remains the most common malignancy in men other than skin cancer, accounting for 30% of male malignancies.[1] The incidence in the United States is predicted to be 189,000 new cases per year in 2002 and is rising as the population ages. Consequently, it is estimated that one in six men will develop clinically apparent prostate cancer in their lifetime. Overall, the median age at diagnosis is 72, although 9% of all prostate cancer cases present in men less than 55. For unclear reasons, the age-adjusted incidence of prostate cancer per 100,000 African Americans is 234 vs 147 for whites. A particularly high incidence of prostate cancer as well as familial aggregation has been noted in Jamaican men.[2,3] African Americans are typically afflicted at an earlier age and in general have been thought to develop a more aggressive disease with poorer survival. However, more recent research has concluded that stage-for-stage prognosis for Caucasians and African Americans is more similar than previously anticipated,

although African Americans may be at increased risk of biochemical recurrence.[4,5]

Despite its high incidence, surprisingly little is actually known about the etiology of prostate cancer. Several risk factors including age, family history, race, dietary fat intake, and hormone exposure have been identified.[6] Nevertheless, a definitive genetic and cellular mechanism has yet to be determined and has been the focus of much research over the past two decades. As the mechanisms of carcinogenesis for other tumors have been elucidated, increasing efforts have been placed on unearthing similar pathways in the prostate. Several institutions have begun to identify families with an increased incidence of prostate cancer to perform segregation and linkage studies. Because of its high overall incidence, significant progress in identifying candidate regions or genes for increased prostate cancer has required a collaborative effort between several institutions. Together, these efforts have yielded many clues toward identifying a genetic predisposition for prostate cancer but continue to leave many persistent questions.

Patterns of Inheritance

Autosomal Dominance

The initial indications that a genetic component might exist in the transmission of prostate cancer came with the discovery of familial clustering of the disease. This was first reported in 1956, when Morganti et al. showed that relatives of patients with prostate cancer had a higher chance of contracting the disease vs controls with no afflicted relatives.[7] Familial clustering was also noted through the Utah Mormon genealogical database.[8] This increased risk was later confirmed in several other studies and quantified in two studies done in the early 1990s. A group of 385 patients in Texas with histologically confirmed adenocarcinoma of the prostate were compared against a similar group of control patients looking for a significantly different family history.[9] The affected patients were found to have a positive family history 13% of the time vs only 5.7% in the controls. The odds ratio for prostate cancer in a man with an affected first degree relative therefore was calculated to be 2.4. Similarly, Steinberg et al. reported that the relative risk of contracting prostate cancer increased as the number of affected first-degree relatives increased.[10] More specifically, patients with two or three affected first-degree relatives were found to be 5 or 11 times, respectively, more likely to contract the disease themselves.

Evidence of a genetic component to prostate cancer has also been seen in twin studies. Gronberg et al. reported the incidence of prostate cancer in 4,840 male twin pairs followed in an unselected Swedish population.[11] Prostate cancer was diagnosed in 458 male twin pairs, with 1.0% rate of monozygotic twins and 0.2% rate of dizygotic twins concordant for prostate cancer. Similarly, 1,009 cases of prostate cancer from a cohort of 31,848 veteran twins were identified by Page et al.[12] The concordance rate among monozygotic twins was 27.1% compared to 7.1% for dizygotic twins, again suggesting a genetic element for increased risk of developing prostate cancer.

With strong evidence for familial clustering established, the next step was to ascertain if a hereditary component for the development of prostate cancer existed. This distinction was made to specifically look for those families with prostate cancer that demonstrated a mendelian pattern of distribution.[13] To test for the existence of a mendelian pattern of inheritance, segregation analysis was performed on families with probands who had early-onset disease. The hypothesis was that early disease onset would be more associated with a genetic or heritable component. The landmark article in this area was published in 1992 from Johns Hopkins University.[13] In this study, 691 prostate cancer families were analyzed for the frequency and pattern of distribution of prostate cancer and evaluated for various models of transmission. These included the following five models: a sporadic model, where persons of the same age would have the same risk; an environmental model, where a nongenetically determined risk would be accounted for; and three Mendelian models, specifically autosomal dominant, autosomal recessive, and codominant. The model that best fit their data for familial clustering of early onset prostate cancer was that of an autosomal-dominant, highly penetrant allele. Eighty-eight percent of patients with this allele would be afflicted with disease by age 85 vs 5% of men without the allele. Carter et al. estimated that this heritable form of prostate cancer accounts for 43% of early-onset disease (<55 years) but only 9% of all prostate cancer.[14]

Three subsequent studies have used similar approaches in different populations to attempt to confirm Carter et al.'s results.[11,15,16] All three groups found that an autosomal-dominant model best fit their data for transmission of early onset prostate cancer, although there was some discrepancy in the degree of penetrance and the expected frequency of the allele. For instance, the first of these confirmatory studies was drawn from over 5,000 Swedish men diagnosed with prostate cancer in the early 1960s. While the authors agreed that an autosomal-dominant allele was most likely, a lower lifetime penetrance (0.63 vs 0.88) and a higher frequency (0.0167 vs 0.0030) were estimated compared to Carter et al.[11] Conversely, a recent study out of Washington University predicted a higher lifetime penetrance, with 97% of allele carriers being afflicted by the age of 85.[16] The authors proposed that this allele accounts for as much as 65% of early-onset prostate cancer (<55 years) but only 8% of total disease. In summary, these studies have concluded that an autosomal dominant, variably penetrant allele, is involved in the transmission of between 43% to 65% of early-onset prostate cancer cases but <10% of overall cases. Genetic complexity, with multiple involved genes and a high number of phenocopies, likely accounts for the disparity in numbers seen between these various studies. Therefore, it is important to inquire about prostate cancer from both the paternal and maternal family histories.

X-Linked Transmission

Evidence for transmission of an X-linked pattern of transmission has also accumulated over the past several years. This was first hypothesized after the observation that a twofold greater age-adjusted relative

risk existed for the contraction of prostate cancer in men with an affected brother vs men with an affected father.[17] This difference in relative risk therefore was attributed to a possible X-linked allele. However, although this theory never actually disproved, rather than an X-linked allele some authors have attributed this increased risk to underreporting by the fathers, who were often without the benefit of early detection modalities such as prostate-specific antigen (PSA).[15] As will be seen, though, further strong evidence for an X-linked pattern of transmission has more recently become available.

Age and Inheritance

Similar to the number of affected relatives, the young age of affected relatives has been shown to increase the relative risk of developing prostate cancer. Carter et al. have shown that the lifetime risk of developing prostate cancer for men with a relative who developed prostate cancer before the age of 53 is 40% while the risk is only 18% with a relative who develops prostate cancer after the age of 65.[14] Therefore, taken in combination, the father or brother of an affected 40-year-old male has a 2.6-fold relative risk of prostate cancer compared to a 10- to 11-fold increased risk if two first-degree relatives are affected.

Prostate Cancer and Other Tumor Types

Not only have individual cancers been noted to occur at increased frequency within families, but cancer syndromes in which several tumor types cluster within families have also been identified. Epidemiological studies have suggested a link between breast and prostate cancer for many years.[13,18] In addition, case control studies have demonstrated an association between breast carcinoma and prostate carcinoma and possibly with endometrial and ovarian cancer.[19] Upon further analysis, risk of prostate cancer did not appear to be modified by the presence of breast cancer within a pedigree of prostate cancer.[20] However, a statistically significant higher risk for central nervous system tumors was found (relative risk [RR], 3.02). Therefore, despite previously conceived associations, hereditary predisposition to prostate cancer appears to be relatively site specific.

In summary, prostate cancer has definitely been shown to cluster in families and demonstrate an autosomal-dominant pattern of inheritance as well as an X-linked pattern of transmission. In addition, the closer the genetic similarities between an individual and an affected relative (e.g., father and son vs an uncle), the greater the risk of developing prostate cancer. Overall, approximately 9% of prostate cancer has been estimated to be hereditary.

Potential Alleles

To identify the specific gene or genes that may be involved in the transmission of early-onset prostate cancer, researchers have focused on families with particularly high numbers of affected individuals. Sixty-six families with at least three cases of prostate cancer among first-degree relatives were identified at Johns Hopkins Hospital.[21] The average age at diagnosis in these families was 65. An analysis of these

families was performed utilizing 341 dinucleotide repeat markers with an approximate 10cM resolution. Linkage analysis was then performed, identifying several regions with genetic load scores suggesting linkage. The highest *load* score (2.75) was for marker *D1S218*, which maps to the long arm of chromosome 1 *(1q24–25)*. The authors designated this locus as hereditary prostate cancer 1 (*HPC1*), estimating that as many as 34% of heritable prostate cancer cases were linked to this locus. Other regions from this analysis with load scores >1 were *1q33–34, 4q26–27, 5p12–13, 13q31–33,* and *Xq27–28*. To further define the location of *HPC1*, linkage of the *1q24–25* region has been investigated in 121 North American hereditary prostate cancer families utilizing a set of markers with higher resolution.[22] The peak load score was 4.27 at marker *D1S2138* but over a broad region. Therefore, subset analyses have been performed that suggest that: (1) 35% of the families demonstrated highly significant linkage to this region (load score 5.41), while the remaining families did nor; (2) evidence for linkage to this region was highest in families with five or more affected family members; and (3) linkage to this region was highest in families with apparent male-to-male transmission.

Independent investigators have both confirmed and failed to confirm *HPC1* as a susceptibility locus for prostate cancer. Cooney et al. reported linkage to *1q24–25* in 59 prostate cancer families, each with 2 or more affected individuals,[23] Hsieh et al. in 92 unrelated families,[24] and Neuhausen in 44 large pedigrees in Utah.[25] However, three other groups have not found linkage to *HPC1* in their populations.[26–28] The reason for disparity between analyses has been attributed to several factors including genetic locus heterogeneity, the number of men within families, their age of diagnosis, and the variability of male-to-male transmission. To increase the power to confirm or disprove linkage to the *HPC1* locus, the International Consortium for Prostate Cancer Genetics, including investigators from North America, Australia, Finland, Norway, Sweden, and the United Kingdom, performed a combined analysis of 772 hereditary prostate cancer families utilizing six markers in the *1q24–25* region.[29] Overall, there was confirmation of some linkage to *D1S212*; however, it was primarily in the subset of families with multiple family members affected at an early age and with male-to-male transmission.

Although region *1q24–25* of chromosome 1 has probably received the most intense investigation for a prostate cancer susceptibility locus, numerous groups have presented evidence for a variety of other susceptibility loci in other regions of chromosome 1. This has not been unexpected considering that prostate cancer remains a heterogeneous tumor type with variable clinical significance and rates of progression. A French study identified a different region on the long arm of chromosome 1 at *1q42.2–43,* which has been designated *PCaP*.[30] Several genes have been mapped to this region, which lends credence to the argument for a susceptibility locus. The most notable of these are *PCTA1*, a member of the galectin family that has been implicated in tumor genesis and metastasis,[31] poly (adenosine diphosphate [ADP]-ribose) polymerase, which has been implicated in lung cancer,[32] and

RAB4, a guanosine triphosphate (GTP)-binding protein.[33] In addition, region *1p36* has been implicated and a gene locus designated *CAPB*.[34] Subset analysis of families with linkage to *1p36* in this study demonstrated an association between prostate cancer and brain cancer, leading to the hypothesis that this region contains a general tumor suppressor gene, the loss of which predisposed to both prostate and brain cancer.

Evidence for an X-linked susceptibility to prostate cancer has been proposed as outlined above. In the original study by Smith et al. proposing linkage to the *HPC1* locus, the X chromosome region q27–28 was also implicated.[21] Subsequently, analysis of 360 prostate cancer families in North America, Finland, and Sweden confirmed linkage and designated this as hereditary prostate cancer X (*HPCX*).[35] In a confirmatory study, a group of 153 unrelated families was analyzed utilizing seven markers spanning the proposed *HPCX* region.[36] Although the level of significance was not high, additional support for an X-linked predisposition to prostate cancer was observed. Although the androgen receptor gene is located on the X chromosome and would be a likely candidate to demonstrate linkage, it is remote from this region. Consequently, no specific genes have been identified at the *HPCX* locus yet.

Other studies suggested linkage to regions of several other chromosomes including chromosome 20. Berry et al. proposed a hereditary prostate cancer 20 locus (*HPC20*) at *20q13*.[37] A locus on chromosome 17 designated hereditary prostate cancer 2 (*HPC2*) has also been identified.[38,39] More recently, chromosome 8p, which has been implicated in the development of prostate cancer for many years, has shown linkage at *8p22–23*.[40]

In summary, there have been, to date, seven prostate cancer susceptibility loci identified by linkage analysis: *HPC1*, *HPC2*, *HPCX*, *HPC20*, *CAPB*, *PCaP*, and *8p22–23*. None of these loci has been uniformly accepted, and controversy continues as to the importance of potential genes located at each locus. The true percentage of cases that can be attributed to each is also undetermined, but it has been speculated that the sum of these loci may account for a mere one third of the total heritable cases.[37] This further emphasizes that the etiology of prostate cancer is complex, with a myriad of factors, both genetic and environmental, likely contributing to its development and transmission.

Specific Alleles

Androgen Receptor and Androgen Action

Polymorphisms of the androgen receptor have been reported to play a contributing role to the development of prostate cancer. Polymorphic triplet sequences in exon 1 of the androgen receptor code either for polyglutamine (CAG) or polyglycine (GCN) repeats of variable length. The length of the polyglutamine repeat region has been shown to inversely correlate with the transcriptional response of androgen regulated genes.[41–43] Studies to investigate potential correlations between variable triplet repeat regions and prostate cancer risk demonstrated

that African American populations, who have increased risk of prostate cancer development, have shorter glutamine repeat regions.[44–46] However, several studies failed to observe a similar correlation; therefore, these studies have not been entirely conclusive. A more recent report evaluating 159 hereditary prostate cancer probands, 245 sporadic prostate cancer cases, and 211 unaffected controls has concluded that variation in GGC repeats rather than CAG repeats was primarily responsible for increased prostate cancer risk.[47]

More recently, polymorphisms of genes involved in androgen metabolism have been implicated in susceptibility to prostate cancer. 3β-hydroxysteroid dehydrogenases (HSD3Bs) are involved in the production of androstenedione and conversion of dihydrotestosterone into inactive metabolites. The two genes in the HSD3B family map to chromosome *1p13,* which has shown linkage for prostate cancer susceptibility.[40,48] Men with variant genotypes at either B1-N367T or B2–c7519g were found to have a significantly higher risk of developing hereditary prostate cancer. Further, it was determined that prostate cancer probands whose families provided the primary evidence of linkage to *1p13* demonstrated variant genotypes. Similarly, polymorphisms in the *CYP17* gene that encodes cytochrome P-450c17α, which is also involved in the androgen synthesis pathway, may modulate susceptibility to prostate cancer.[49–52]

BRCA1 *and* BRCA2

As noted above, epidemiological studies suggested a link between prostate and breast cancer for many years. Since their identification, several studies demonstrated an increased risk of prostate cancer in association carriers of mutations in *BRCA1* and *BRCA2*.[53–56] Several other studies have not been as supportive of a strong association between *BRCA1* and *BRCA2* mutations and the development of prostate cancer. Therefore, although mutations appear to contribute to the development of early onset prostate cancer, a complete understanding of the contribution remains to be delineated.

Other Alleles

As genes with significant numbers of mutations or abnormalities of expression in prostate cancer are identified, characterization of individual variation in alleles may yield information regarding possible germline transmission of prostate cancer susceptibility. For example, inactivation of the tumor suppressor *PTEN/MMAC1* in advanced prostate cancer has been demonstrated in at least 50% of cases.[57] However, this has not been attributed to heritable gene mutations, deletions, or polymorphisms.[57,58] Future identification of other somatic genes with frequent alterations in expression during prostate cancer initiation or progression may be shown to be significant heritable factors through linkage analysis.

Clinical Implications

Significant progress has been made in genetically confirming previous clinical impressions that some families are at increased risk for the de-

velopment of prostate cancer. It has now been well established that familial clustering does exist, and that primary relatives of prostate cancer patients are at greater risk of developing prostate cancer themselves than the general population. In general, approximately 25% of men are expected to have a known family history of prostate cancer. However, one should be aware that family history of prostate cancer may be incorrect as much as 14% of the time.[59] Through studies of well characterized patient populations, hereditary prostate cancer is estimated to account for 43% of men who are diagnosed at age <55, 34% of men <70, and only 9% of men diagnosed under 85.[20]

Although still controversial, prostate cancer screening is in general recommended for men after reaching the age of 50 and potentially earlier if an individual has a significant family history of prostate cancer or is African American.[60] This practice would seem advisable to hopefully detect tumors at an early age, at their earliest stage, when they should have the highest likelihood of cure. This concept is already in practice in breast cancer families with a known predisposing *BRCA1* allele. However, it is interesting to note that men with hereditary prostate cancer have in general been found to develop prostate tumors that are moderately well differentiated and of no greater biologic potential than sporadic prostate cancer.[61–63] As specific genes within current candidate loci are identified and characterized, it will potentially be possible to screen populations for genotypes leading to more biologically aggressive prostate cancers who may benefit most from focused chemoprevention or early treatment options.

Wilms' Tumor (Nephroblastoma)

Incidence

Wilms' tumor is named for Max Wilms, who characterized features of the malignancy in 1899. In the years subsequent, Wilms' has been one of the most well-studied tumors and has provided invaluable information about the genetic mechanisms of carcinogenesis. While its overall incidence is relatively rare, Wilms' is the most common malignancy in children less than age 15. In fact, it accounts for 8% of all pediatric solid tumors and 80% of pediatric genitourinary malignancies. There are approximately 450 cases diagnosed in the United States per year. The male to female ratio is essentially equal, and the average age of diagnosis is between 3 and 4.[64,65]

Patterns of Inheritance

The first attempts to explain the transmission of Wilms' tumor were made by Knudson in the early 1970s. In 1971, Knudson proposed a "two-hit hypothesis" as a potential mechanism for tumor genesis.[66] He suggested that the loss of both alleles of a tumor suppressor gene would lead to the development of cancer. He used retinoblastoma in his original model. His theory stated that individuals with familial disease inherited a defective gene, leaving them with only one functional allele.

A somatic mutation would then occur as a random event during normal cell proliferation. The cell would then be left with no functioning protein product from the tumor suppressor gene. The result would be unregulated cell division, overproliferation, and eventually tumor formation. These patients would have earlier age of onset and frequent bilaterality. Knudson went on to say that nonfamilial cases were secondary to two spontaneous random mutations, a much less frequent event, within the same cell. This explained why these patients had only a single, unilateral tumor and a later age of onset.

Knudson attempted to apply this principle to Wilms' tumors. He studied published reports of familial cases as well as 97 cases treated at his own institution.[67] He found that indeed the incidence of bilateral tumors was higher in familial cases, 21% vs 5% to 10%. He also found that familial cases had an earlier age of onset, 2 years vs 3 to 4. By assuming that all bilateral as well as a percentage of unilateral cases were secondary to an inherited component, Knudson calculated that familial cases comprised more than one third of the total case number. Subsequent epidemiological studies of Wilms' tumor patients have shown that familial cases are actually more rare, comprising only 1% to 2.4%.[68,69] These observations suggested that the genetic transmission of Wilms' tumor was more complex than retinoblastoma and likely involved multiple genes.

Associated Abnormalities

Early on, it was recognized that Wilms' tumor is associated with various organ system anomalies. The most prevalent of these include aniridia (1.1%), hemihypertrophy (2.9%), genitourinary abnormalities (4.4%), and musculoskeletal anomalies (2.9%).[64] Common combinations of these anomalies have subsequently been clustered into childhood syndromes. The study of children with these syndromes provided the initial evidence toward the genetic etiology of the disease.

In 1964 Miller et al. examined 440 children with Wilms' tumors and found 6 with aniridia, 5 of whom had concomitant mental retardation or microcephaly.[70] The authors calculated an aniridia rate of 1 in 73 vs the expected rate of 1 in 50,000. In addition, children with aniridia were diagnosed with Wilms' tumor at an earlier age. Other abnormalities noted included 34 children with various genitourinary anomalies including hypospadias, cryptorchidism, horseshoe kidney, ureteral duplication, and dysplastic kidneys, and 7 children with either pigmented nevi or hemihypertrophy. WAGR syndrome was later coined to include Wilms' tumor, aniridia, genitourinary malformations, and mental retardation.[71]

A second syndrome was described in 1969 by pediatric pathologist Bruce Beckwith, who reported on six cases of neonatal death. Autopsy examination of the infants revealed macroglossia, omphalocele, visceromegaly, hemihypertrophy, and renal medullary dysplasia.[72] A short time earlier, a second researcher named Wiedemann reported similar findings in three siblings of consanguineous parents.[73] This combination of findings was therefore named the Beckwith-

Wiedemann syndrome. It is now known that Beckwith-Wiedemann consists of visceromegaly of the liver, kidneys, adrenals, pancreas, and gonads, as well as frequent macroglossia, omphalocele, hemihypertrophy, and retardation. Tumors, including Wilms', are seen in approximately 10% of the cases.[74] While most cases of Beckwith-Wiedemann are sporadic, approximately 15% are familial with an apparent autosomal dominant transmission.[75]

A third syndrome was subsequently described independently by two different investigators and named Denys-Drash syndrome after its discoverers.[76,77] Findings of this syndrome include Wilms' tumor, pseudohermaphroditism, hypertension, and degenerative renal disease. Denys-Drash is overall a rare disorder, with only about 150 cases reported in the literature. The mortality of the syndrome is severe, most typically from end-stage renal disease.[78]

Specific Alleles

11p13 (WT1)

Studies of patients affected with the WAGR syndrome provided the initial evidence for localization of Wilms' tumor gene 1 (*WT1*). In 1978 Riccardi et al. conducted chromosome analysis on three WAGR patients. In each case, an 11p13 deletion was detected.[79] Subsequent improvements in gene cloning technology permitted the isolation of the *WT1* gene within the *11p13* locus.[80,81] Characterization of the gene revealed 10 exons that undergo alternative splicing during transcription.[82] The predominant splice form encodes a protein product containing four zinc finger domains with significant homology to known transcriptional regulators *EGR1* and *EGR2*.[81,82] These findings suggested that *WT1* might serve as a tumor suppressor gene, the loss of which would result in unregulated cell proliferation. This was later substantiated through a series of in vitro experiments that demonstrated a suppression of growth-stimulating genes by high levels of *WT1*.[65]

Having demonstrated a role for *WT1* in WAGR syndrome, researchers next examined Denys-Drash patients for deletions or mutations. Greater than 95% of children with this syndrome were determined to harbor a *WT1* mutation.[83] The majority of these were point mutations within the zinc finger coding region.[83,84] Current tumor models propose that the mutated allele produces a "dominant-negative" protein that prevents activity of the wild-type allele protein, effectively inactivating the normal zinc finger protein and leading to aberrant cell proliferation.[84,85]

These findings implicated mutations in *WT1* as the etiology for WAGR and Denys-Drash syndromes. Kreidberg et al. provided further evidence for this by demonstrating that *WT1* is critical for early urogenital development.[86] But, because these syndromes account for less than 10% of total Wilms'cases, sporadic tumors required additional analysis. *WT1* mutations were found in only 5% to 10% of sporadic cases.[83,84] This was a clear indication that other genetic etiologies must be involved in Wilms' tumor development, thereby requiring further investigation.

11p15 (*WT2*)

Shortly thereafter, a second locus involved in the development of Wilms' tumor was identified. Chromosome analysis on sporadic Wilms' tumors revealed significant loss of heterozygosity in a number of tumors at *11p15,* with no loss noted at the *11p13* locus. From this it was hypothesized that a second tumor suppressor gene might reside at the *11p15* locus. A putative gene within this locus was designated Wilms' tumor 2 (*WT2*).[87,88] Concurrent studies were also being done at this time with familial Beckwith-Wiedemann families. Linkage analysis of these families revealed significant linkage to the *11p15.5* locus.[89,90] It was not known at that time if a single gene at this locus controlled the development of both Beckwith-Wiedemann syndrome and Wilms' tumor or if separate unrelated genes existed.

Through the efforts of several investigative groups, three candidate genes have been cloned within the *11p15* locus. The first was insulin-like growth factor II (*IGFII*), an embryonal growth factor that induces cell proliferation. *IGFII* is an imprinted gene with only the paternal allele being expressed in humans. Expression of *IGFII* has been shown to be markedly increased in Wilms' tumors relative to adult tissues.[91] The overexpression has been attributed to either relaxation of imprinting or loss of the maternal allele and paternal duplication.[92] The second gene, *H19*, also displays imprinting but with expression of only the maternal allele. *H19* has been experimentally transfected into tumor cells and shown to cause growth retardation. For this reason, it has been implicated as a tumor suppressor gene.[93] Loss of function of *H19* may be secondary to either loss of heterozygosity (LOH) or hypermethylation of the maternal allele.[94] The third gene, *KIP2*, has also demonstrated paternal imprinting. *KIP2* is a cyclin-dependent kinase inhibitor involved in cell cycle regulation. Expression of *KIP2* has been shown to be decreased in Wilms' tumor cells relative to adult tissues.[94,95]

The interplay of these genes in the development of Wilms' tumor and Beckwith-Wiedemann syndrome still remains unclear. Loss of *H19* and overexpression of *IGFII* may be required together, independently, or not at all. Other currently unknown genes may be involved as well. Further research is required to definitively establish how these genes are involved in the etiology of these disorders.

Potential Alleles

In addition to the loci identified on chromosome 11, evidence for other loci involved in Wilms' tumor development exists as well. For instance, linkage analysis of two pedigrees with familial Wilms' tumors demonstrated no linkage to either *WT1* or *WT2*, implicating the probable existence of a third locus.[96] Candidate chromosomes for this locus include 16q, 7p, and 17p.

The long arm of chromosome 16 gained initial interest in 1992, when Maw et al. demonstrated LOH on 16q in 9 of 45 sporadic tumors.[97] A follow-up study confirmed the association and also noted that those tumors with 16q LOH had a 3.3 times higher relapse rate and a 12 times higher mortality.[96] For this reason some authors proposed that 16q may

harbor genes involved with tumor progression rather than initiation.[65] Miozzo et al. examined 11 sporadic tumors and found a significant number of LOH on chromosome 7p. Of these 11, one had a rearrangement at *7p15.5.* This provoked the authors to implicate that region as a potential tumor suppressor gene.[98] Linkage has also been demonstrated for a familial gene on chromosome 19q, although this presence has not been confirmed in all studies.[99,100]

Finally, the *p53* gene on chromosome *17p* has been implicated in Wilms' tumor development as well. This is not surprising, as *p53* is known to be involved in multiple neoplasms including breast and colon cancer. Utilizing polymerase chain reaction, Malkin et al. identified two mutations within the coding region of *p53* in 21 tumors. The two tumors were both advanced in stage, leading to the conclusion that a relationship between *p53* abnormalities and tumor severity may exist.[101] Further evidence for this was provided by Bardeesy et al., who found *p53* mutations in 8 of 11 anaplastic Wilms' tumors, a known variant with a poor prognosis.[102]

In summary, Wilms' tumor is a genetically complex disease with multiple factors and loci contributing to its development. *WT1* appears to be involved in the majority of Wilms' tumor cases associated with anomalies of the genitourinary tract, as seen in WAGR and Denys-Drash syndromes. Overall, though, *WT1* mutations are seen in less than 10% to 20% of all cases. *WT2* has been implicated as a region controlling not only Wilms' tumor development but Beckwith-Wiedemann syndrome as well. Three genes have been isolated at *WT2*, all of which may be involved in carcinogenesis either through overexpression or inactivation. In addition, evidence exists for the involvement of several other loci. One or more of these may be involved in controlling tumor progression and severity.

Clinical Implications

The information gained from research in Wilms' tumor may ultimately be applied to clinical screening practices. However, at this time it is probably not advantageous to screen siblings of affected children, as the familial incidence is so low. However, children with morphological abnormalities or genitourinary anomalies should be watched closely. A history of WAGR, Beckwith-Wiedemann, Denys-Drash, or even sporadic aniridia should raise a particularly high index of suspicion. Patients with Wilms' tumor-associated syndromes should have regular physical examinations and probably renal ultrasounds every 3 to 6 months until age 7.[103,104] Screening for 11p deletions may be considered, but the clinical utility and implications remain in evolution.

Renal Cell Carcinoma

Incidence

Renal cell carcinoma is the most common renal malignancy and accounts for approximately 3% of all cancers. There are roughly 28,000

new cases per year in the United States and 11,000 renal cell-related deaths per year. Renal cell carcinoma most classically afflicts adult, male, urban dwelling patients. There is a 2:1 male to female sex predilection. The typical age of onset is 60 to 70, although there is a subpopulation that develops earlier onset disease, usually between age 40 to 50.[105] The incidence of renal cell carcinoma has been increasing at a rate of 3% a year in North America and Europe, in particular within the African American population.[106] Established risk factors for the contraction of renal cell carcinoma include cigarette smoking, obesity, hypertension or antihypertensive medications, and a diet low in fruit and vegetables.[106] Family history is a suspected risk factor as cases of familial clustering have been reported. Many of these families with multiple affected members are known to have Von Hippel-Lindau disease (VHL), of which early-onset renal cell carcinoma is a well-known component. But, in addition, cases of familial clustering have been well documented in non-VHL families. It is these families, as well as those with VHL, who have provided information and evidence leading to isolation of genetic components involved in renal cell carcinoma development.

Specific Alleles

3p14–p12 *Loci*

The first cancer family to be well studied was in 1979 at the Harvard Medical Center in Boston.[107] Ten members in three successive generations were afflicted with renal cell carcinoma. The cancer occurred at an early age (average 46 years) and was bilateral in 6 of the 10 patients. There was no evidence for VHL. Karyotype analysis of peripheral leukocytes was done on 22 adult members of this family. Of these 22, 8 had documented renal cell carcinoma either from autopsy analysis or surgical specimen. Karyotyping was not done on the 2 other affected family members. Of these 22 patients, 10 were found to have a balanced reciprocal translocation between chromosomes 3 and 8. In addition, the translocation was assigned to 4 deceased relatives based on pedigree analysis. All 8 of the affected family members had the translocation. The remaining 4 living members with the translocation but without evidence of disease were all under age 35, younger than the expected time of onset of disease. From these observations the authors concluded that the presence of this translocation conferred an 87% risk of developing renal cell carcinoma by age 59. A second group of investigators later looked at this same family and did banding analysis of translocations. Breakpoints were found at *3p14.2* and *8q24.1*.[108] These studies provided strong evidence toward the existence of a renal cell carcinoma gene at one of these two loci.

Multiple studies in subsequent years contributed increasing evidence that the gene or genes of interest were located on the short arm of chromosome 3. Of these studies, group of German investigators conducted the largest two. Kovacs et al. cytogenetically analyzed tissue from sporadic, nonhereditary renal cell carcinomas.[109,110] Between 86% to 88% of tumors were found to contain some abnormality of chromosome

3p, either a deletion, nonreciprocal translocation, monosomy, or loss of the short arm of the chromosome. These results supported a hypothesis that a recessive "cancer gene" resided on the short arm of chromosome 3.

This theory was later tested in vitro by a Japanese group that transferred a line of renal carcinoma cells an intact *3p* chromosome.[111] The cells were then introduced into a population of nude mice and their growth characteristics observed. Chromosome 3p expression led to suppression of tumorigenicity and a decreased tumor growth rate vs controls. This experiment was later repeated using fragments of chromosome 3. This localized the suppressive region to the chromosome *3p14–p12*.[112]

As cloning technologies improved over the next several years, closer analysis of this locus became possible and several putative tumor suppressor genes were localized. A Japanese group identified the fragile histidine triad (*FHIT*) gene, which spanned the previously isolated breakpoint *3p14.2* and was found to be abnormal in several tumor cell lines.[113] A second gene, *wnt5a*, was also mapped to this region and found to cause in vitro growth suppression when transfected into human renal carcinoma cells.[114] Finally, two narrow loci, *NRC1* and *NRC2*, were identified and believed to be independent of the aforementioned genes. These loci have also demonstrated growth suppression in vitro, but specific genes have not yet been identified.[115,116] The exact role of these genes, if any, in renal carcinogenesis is not yet fully elucidated.

***Von-Hippel-Lindau Disease*—3p25**

In addition to these studies, other investigative groups were concomitantly looking at families afflicted with VHL, which is an autosomal-dominant disorder. Expected changes include renal cell carcinomas, retinal angiomas, cerebellar hemangioblastomas, pheochromocytomas, and cystic lesions affecting the pancreas, kidney, and epididymis.[117] Presentation of the disease varies widely from patient to patient and may include all manifestations or only a single lesion. The most frequently used clinical criteria require a single lesion and a documented family history to assign the diagnosis of VHL.[118] Approximately 25% of VHL patients develop renal cell carcinoma by age 38. The cancerous lesions in these patients are typically bilateral, multifocal, and of early onset.[119] For these reasons the genetic mechanisms involved in the transmission of VHL were of great interest to those studying the general etiology of renal cell carcinoma.

In 1988, the *VHL* gene was first mapped to the short arm of chromosome 3.[120] Soon after, linkage analysis with multiple markers specific for 3p localized the *VHL* gene to *3p25–p26* and then specifically to *3p25*. While this locus was in close proximity to the previously discovered region at *3p14–p21,* they were in fact two separate and distinct entities.[120,121] The gene and its protein product from this region were soon isolated and dubbed the *VHL* tumor suppressor gene.[122] The protein was found to bind to a cellular transcription factor and inhibit transcriptional activity in vitro.[123,124] It was at this point hypothesized that

the *VHL* locus contained a distinct tumor suppressor gene, the loss of which led to the development of renal cell carcinoma.

To test this theory, the "two-hit hypothesis" proposed by Knudson discussed above was applied. If the *VHL* gene were indeed a tumor suppressor gene, then a high rate of mutation and LOH would be expected within tumor cells. This rate was quantified in primary sporadic renal cell carcinomas by two independent investigators. The studies yielded similar results, finding LOH of the *VHL* gene in 84% and 98% of cases and somatic mutations within *VHL* in 56% and 57% of cases.[125,126] The authors proposed that the number of mutations might actually be an underestimation as the entire gene sequence was not available to them at the time of analysis. These changes were found only in the clear cell type of renal carcinoma. None of the other types (granular cell, tubulopapillary, sarcomatoid, or chromophobe) were found to have *VHL* mutations. The authors therefore concluded from these results that loss of the *VHL* tumor suppressor gene was a key step in the development of both familial and sporadic clear cell renal carcinoma.

Candidate Alleles

3p21–p22

In addition to the two regions mentioned above, evidence has also implicated a third region on chromosome 3p in the development of renal cell carcinoma. A Japanese study analyzed 40 sporadic renal cell carcinomas for loss of heterozygosity of the short arm of chromosome 3. This differs from the VHL study, which looked for LOH specifically at the *VHL* gene in clear cell tumors only. These investigators found LOH in 79% of cases, most frequently at *3p13–p14* and *3p21.3*. This first locus was already under suspicion as a tumor suppressor gene, as discussed above, and the authors now speculated that the *3p21–p22* contained a separate tumor suppressor gene as well.[127] Of interest are two gene products that have been mapped to this region. The first is acylpeptide hydrolase (*APH*), which has been shown to be decreased in amount in renal carcinoma cells vs normal renal cells. It has been speculated that this may act as a tumor suppressor gene by regulating the activity of an acetylated growth factor.[128] The second is transforming growth factor beta receptor (*TGFβR2*), which is a known regulator of cellular proliferation.[129] Again, the exact role of these genes will require further investigation.

Hereditary Papillary Renal Cell Carcinoma and Birt-Hogg-Dube Syndrome

Hereditary papillary renal cell (HPRC) carcinoma is a rare histological subtype that has recently been found to aggregate in certain families. This was first described by Zbar et al., who examined three generations of one family and found nine members with multiple, bilateral papillary renal carcinomas.[130] The authors found no LOH or significant linkage to chromosome 3p. This observation was later confirmed as a nonrandom occurrence with the description of nine additional families with multiple affected members.[131] Cytogenetic analysis of various papillary tumors, both sporadic and hereditary, revealed a frequent

occurrence of trisomy 7, 16, and 17. It was proposed that a proto-oncogene may reside on one or more of these chromosomes and trisomy may lead to overexpression and tumorigenesis.[132,133] To test this hypothesis, Schmidt et al. conducted linkage analysis on nine families with HPRC and found evidence suggesting linkage to *7q31–q34*. The *MET* proto-oncogene was known to reside in this region. The authors then tested blood and tumor samples from affected family members and found various missense mutations within the *MET* genotype.[133] The mutations in the *MET* gene were found to cause increased kinase activity in vitro and to be tumorigenic in mice.[134] These studies provided strong evidence implicating the MET gene in the etiology of HPRC. To test if this was true in sporadic cases as well, 129 sporadic papillary tumors were screened for mutations in *MET*. Mutations were found in only 17 of the cases, prompting investigators to search for a different mechanism for the development of sporadic papillary tumors.[135] Because of the high incidence of trisomy 17 as well as trisomy 7 in papillary renal cell carcinoma, Balint et al. conducted linkage analysis on chromosome 17 in both sporadic and hereditary cases. Significant linkage to the *17q21* locus was identified, implicating a second gene in this region responsible for papillary tumors.[136] Whether such a gene is responsible for the majority of sporadic papillary renal carcinomas will require further investigation.

Another syndrome that has prompted investigation into the etiology of papillary renal carcinomas is Birt-Hogg-Dube syndrome.[137] This syndrome was first described in 1977 by the three investigators for which it was named. The original report described an autosomal-dominant dermatologic condition characterized by the triad of multiple fibrofolliculomas, trichodiscomas, and acrochordons. It was subsequently discovered that, in addition to the cutaneous manifestations, affected patients often had renal tumors and lung disease. To identify and quantify these renal tumors, Toro et al. examined families afflicted with VHL, HPRC, renal cell carcinoma associated with a *3p14* translocation, papillary renal cell carcinoma not associated with a *MET* mutation (nonhereditary papillary renal cell carcinoma), or renal oncocytomas and examined them for signs of Birt-Hogg-Dube syndrome.[138] Two of the renal oncocytoma families and one third of the families with nonhereditary papillary renal cell carcinoma exhibited Birt-Hogg-Dube syndrome, suggesting that the majority of renal tumors found in Birt-Hogg-Dube syndrome were nonhereditary papillary renal cell carcinomas. A recent study conducted linkage analysis on a large Swedish family with Birt-Hogg-Dube syndrome and identified a region on chromosome *17p12–q11.2* with strong evidence of linkage.[139] It is interesting to note that this region is in close proximity to the locus found by Balint et al.[136] More conclusive statements about the etiology of sporadic papillary renal cell carcinoma will be possible as genes and gene products from this region are isolated.

Other Potential Loci

In addition to the regions mentioned previously, evidence that other loci may be involved in the development of renal cell carcinoma as well

has been reported. Morita et al. analyzed 64 sporadic renal cell carcinomas for common deletions using markers specific to chromosomes *5p, 6q,* and *10q*. Loss of heterozygosity of *5q* was found in 33%, *6q* in 39%, and *10q* in 41%. Deletion maps were constructed narrowing the loci of interest to *5q21, 6q27,* and *10q21–23*. While LOH was not as frequent as with chromosome *3p,* the authors believed it to be significant.[140] Of these loci, the *5q21* is most interesting as it is known to contain the two tumor suppressor genes mutated in colorectal cancer (*MCC*) and adenomatous polyposis coli (*APC*). The inactivation of these genes has been associated with multiple gastrointestinal malignancies including colorectal, esophageal, and gastric carcinomas. Suzuki et al. therefore looked specifically at the LOH of these two genes.[141] *MCC* LOH was found in 18.2% and *APC* LOH in 14.3% of sporadic renal cell carcinomas evaluated, demonstrating that loss of these genes was an infrequent event in the development of renal cell tumors.

Two other regions that have attracted interested are *9q34* and *16p13*. These are the loci for the two tumor suppressor genes *TSC1* and *TSC2*, which are involved in the development of tuberous sclerosis.[142] Renal cell carcinoma has been shown to be weakly associated with tuberous sclerosis, with approximately 30 reported cases between 1980 and 1996. In addition, it has been shown that specific mutations in the *TSC2* homolog in rats predisposes them to renal cell carcinoma.[143,144] One study from the Mayo Clinic examining six cases of renal cell carcinoma in tuberous sclerosis patients found that the average age of onset was 36 years, and three of the six had *9q* or *16p* LOH. The authors concluded from this that inactivation of the *TSC* tumor suppression genes may contribute to the development of renal cell carcinomas.[145]

Conclusion

In summary, several regions with putative tumor suppressor genes have been associated with the development of renal cell carcinoma. The three main regions are on chromosome *3p: 3p14–p12, 3p25,* and *3p20–21*. Isolated and suspected tumor suppressor genes at these regions include *FHIT*, *wnt5a*, *VHL*, *APH*, and *TGFβR2*. A subset of renal cell cancers, papillary tumors, has been associated in the hereditary form with the proto-oncogene *MET* on chromosome 7. There is some evidence that sporadic papillary tumors and those associated with Birt-Hogg-Dube may be secondary to mutations on chromosome 17. Finally, it has been demonstrated that loci on 5p, 6q, 10q, 9q, and 16p may have an infrequent association with renal cell carcinoma development, in particular at loci for genes *MCC*, *TSC1*, and *TSC2*.

Clinical Implications

The therapeutic implications of this body of research currently surround advanced screening with early detection and treatment. If two or more family members are affected by renal cell carcinoma, further clinical evaluation of other family members may be warranted. Bilateral or multiple renal tumors within an individual should also raise suspicion for a hereditary predisposition. Genetic screening of potentially affected family members can not only lead to early detection of

renal tumors, thereby improving the possibilities for nephron-sparing surgery, but also identify those individuals who may benefit from close monitoring for other manifestations of hereditary tumor syndromes including ophthalmologic or central nervous system lesions. As specific genes are isolated, high-risk families can be quickly identified, and relatives of affected patients can be more accurately screened for disease susceptibility. There is no current gene therapy for renal cell carcinoma, although it is a promising and exciting field as the complex mechanisms of tumor development are further elucidated.

Bladder, Ureteral, and Renal Pelvis Cancer

Incidence

Bladder cancer is the fourth most common cancer in men, after prostate, lung, and colorectal cancer, accounting for 5.5% of all cancer cases. In the United States there are roughly 50,000 new cases with about 11,000 bladder cancer-related deaths per year. Bladder cancer has a predilection for white males, with a 3:1 male:female ratio and a 2:1 white male:black male ratio. Interestingly, there is an equal incidence between black and white females. Overall in women it is the eighth most common cancer, accounting for 2.3% of all cases. The incidence appears to be declining in women whereas it continues to rise in men. The median age of onset is 69 in men and 71 in women, although cases have been reported at all ages. Incidence, aggressiveness, and mortality all increase with age.[146,147]

Between 90% and 95% of bladder cancers are transitional cell tumors. The remaining tumors are typically either squamous cell carcinomas or adenocarcinomas. Transitional cell carcinomas also occur in the renal pelvis and ureter and are considered here as well. Both are uncommon, and they respectively account for only 5% and 1% of total transitional cell carcinomas. Similarly to bladder cancer, both occur more frequently in white males typically, but not exclusively, in patients older than 75. There is some debate about the risk factors for transitional cell carcinoma. Studies have consistently implicated cigarette smoking as well as exposure to aniline dyes as causative agents. There have been both positive and negative reports of increased risk from coffee drinking, analgesic abuse, artificial sweetener use, and chronic cystitis.[148–152]

Epidemiology

Family history was initially believed to be a significant risk factor for development of transitional cell carcinoma after early reports of familial clustering became available. It was not until later, larger epidemiological studies were performed that the notion of a heritable component became equivocal. The importance of family history remains an issue of debate, and evidence both for and against it exists. One of the first reports of familial clustering was in 1967, where one family was found to have four cases of bladder cancer among its immediate members. A father and three of his sons were all affected and at a rel-

atively young age (<65). All four members were heavy smokers. Interestingly, the mother died of adenocarcinoma of the colon, and two of the sons later developed lung cancer. This may indicate a general predilection for cancer rather than a specific bladder cancer inheritance.[153,154] Other reports include a family with six affected members within two generations and another family with three affected siblings. All of the patients in these cases contracted the disease before age 50. As in the first family, these patients also had significant other risk factors such as smoking or occupational exposure to carcinogens.[155,156]

The largest epidemiological study was conducted in the United States in 1985.[148] Nearly 3,000 patients with a histological diagnosis of bladder cancer were compared retrospectively against 5,782 controls. The controls were matched for age and sex only. Questionnaires assessed various risk factors including smoking, occupational exposure, history of cystitis, artificial sweetener use, and any history of a first-degree relative with cancer of the urinary tract. Distinction between bladder and kidney cancers was not determined. A positive family history was found in 6% of the cancer patients vs 4% of the controls. This yielded a relative risk of 1.45 with a confidence interval (CI) of 1.2 to 1.8. The authors went on to note that younger patients (<45 years) and female patients had even higher relative risk, 2.7 and 1.8, respectively. From this data the authors hypothesized that a genetic mechanism may affect patient susceptibility to bladder cancer.

This hypothesis was placed in doubt a year later by a second group of investigators who were unable to confirm the earlier findings.[149] These authors retrospectively reviewed 173 female patients with early onset bladder cancer (20 to 49 years). Only one patient with a first-degree relative with bladder cancer was identified, and two others with relatives with kidney cancer. These findings were not significantly different from their control group. The authors concluded that an affected first-degree relative did not impart an increased risk of contracting transitional cell cancer, directly contradicting the previous study, which found that both female sex and early-onset disease were associated risks.

A third study from Germany looked at 675 patients with bladder, renal pelvis, or ureteral cancers.[150] Along with various other risk factors, the prevalence of a positive family history was examined. A significantly elevated relative risk in men of 2.4 (95% confidence interval 1.2 to 4.7) was noted, but there was no increase seen in females.

One argument for the disparity seen between these studies has been the lack of controlling for known risk factors such as smoking. For instance, a family may have multiple members who are heavy smokers. If there is an above normal incidence of bladder cancer in such a family, it may be attributed to a heritable component when in fact it could be secondary to smoking. For this reason Kramer et al. conducted an experiment controlling for smoking status.[157] Relative risks in both smoking and nonsmoking first-degree relatives of affected patients were examined. An increase relative risk of 1.8 in relatives who did not smoke and an increased relative risk of 2.1 in relatives who did smoke was observed. The authors concluded that a familial component that is independent of smoking does exists.

Kiemeney et al. looked at not only first-degree relatives but second- and third-degree relatives of affected patients.[158] One-hundred ninety patients from Iceland were examined, observing an overall increased relative risk of 1.24 with any affected relative. Interestingly, though, most of the affected relatives were found to be second and third degree rather than first degree. In fact, the risks for having affected first-, second-, and third-degree relatives were 0.96, 1.38, and 1.27, respectively. No increased risk in relatives of younger patients was observed, arguing against a genetic mechanism.

Transitional Cell Carcinoma-Associated Syndromes

From these studies it cannot be determined with certainty if the relatives of patients with a sporadic urothelial tumor manifest a higher RR of developing a carcinoma themselves. It has been convincingly shown, though, that certain syndromes are associated with the development of transitional cell carcinomas. Specifically, these syndromes are Lynch syndrome II and its variant, the Muir-Torre syndrome. Lynch syndromes I and II were first described by Henry Lynch when he recognized two distinct types of hereditary nonpolyposis colorectal cancer (HNPCC).[159] Type I was characterized as early-onset, multiple metachronous, and synchronous proximal colonic adenocarcinomas. It is transmitted via autosomal-dominant inheritance. Type II contains all aspects of type I but in addition is associated with other visceral malignancies, most notably of the ovaries and endometrium. Muir-Torre syndrome is believed to be a variant of Lynch syndrome II that manifests cutaneous lesions in addition to the visceral malignancies. These include sebaceous adenomas, sebaceous epitheliomas, and keratoacanthomas.[159] Originally coined the "cancer family syndrome," it was long believed that Lynch syndrome II was associated with transitional cell carcinomas of the renal pelvis and ureter. One of the first case reports to describe this was from 1985 in a woman with Lynch syndrome II and bilateral transitional cell carcinoma of the renal pelvis.[160] Another report from 1987 described a man with Muir-Torre syndrome who developed multiple recurrent bilateral transitional cell carcinomas of the renal pelvis.[161] Lynch in 1990 looked at four families with Lynch syndrome II and noticed a preponderance of early-onset ureteral and bladder cancers (mean age, 55).[162] The most definitive examination of this association was from Creighton University in 1993.[163] The authors examined 1,300 members from 23 families with HNPCC. The incidence of various malignancies compared to the general population was analyzed without identifying a significant increase in the number of either renal pelvis or ureteral carcinomas.

Potential Alleles

A large body of research exists providing support for potential transitional cell cancer susceptibility genes throughout the genome. Loci have been implicated on multiple chromosomes including *3p, 4p, 4q, 8p, 9q, 11p, 11q,* and *14q*.[164] Of these, deletions involving chromosome 9 have been identified most frequently. Loss of heterozygosity of the long arm of chromosome 9 has been reported in roughly 50% of all transitional

cell carcinomas regardless of stage or grade. Less frequently (7% to 10%) smaller deletions occur. These smaller deletions have permitted the mapping of various loci hypothesized to contain tumor suppressor genes.[165–168] The *9q34* locus is known to encompass *TSC1*, one of the two tuberous sclerosis genes.[167] A second region, at *9q22.3,* is known to contain the locus for Gorlin's syndrome or familial nevoid basal cell carcinoma syndrome.[168] Specific genes have not been identified at many of these loci, although they are believed to contain tumor suppressor genes of some sort. The exact role they play in transitional cell tumorigenesis is still unclear and will require further investigation.

Specific Alleles

In addition to these loci, several established tumor suppressor genes and proto-oncogenes have been implicated in the development of transitional cell carcinoma. Included in these are *RB1*, *p53*, and *CCND1* (cyclin D1).[164] Sidransky et al. found a mutation rate as high as 61% for the tumor suppressor gene *p53* in muscle invasive bladder cancers.[169] Other investigators confirmed the high incidence of *p53* mutations. In addition, it has also been shown that *p53* is mutated more often in the tumors of smokers and those infected with schistosomiasis.[170,171] As with the susceptibility loci mentioned earlier, the exact role of these genes in the development of transitional cell cancers has yet to be fully elucidated.

In summary, it is clear that heritable transitional cell carcinoma exists, at least as part of cancer syndromes such as Lynch II and Muir-Torre. Whether these cancers are also independently inherited continues to be debated. With equivocal epidemiological data persisting, it is impossible to give a definitive answer. Multiple potential loci and genes have been suggested, and some evidence exists for their significance. Whether these alleles are primarily involved in disease transmission, occurrence, or progression will require further research.

Clinical Implications

At this time, few clinical implications from these studies can be proposed. Certainly, it is probably not beneficial to routinely screen individuals with affected relatives as the risk is equivocal and the procedures are invasive and costly. Certainly patients with cancer syndromes should be closely monitored for various visceral malignancies, not only urologic cancers. Such monitoring will be better facilitated as more susceptibility loci are isolated. In the future, identification and characterization of heritable genetic factors may identify therapeutic drug targets and help define those patients at highest risk for progression to muscle-invasive cancers.

Testicular Cancer

Incidence

Testicular cancer is the most common malignancy in men aged 15 to 35. It accounts for 1% to 2% of all male neoplasms. In the United States

there are approximately 5,500 new cases per year. The overall incidence has been increasing from 2 per 100,000 in the late 1930s to 3.7 per 100,000 in the early 1970s. Typical age of onset is 20 to 40, although there is a relative increase in incidence at 0 to 10 years and >60 years as well. White males are affected three times more frequently than black males. In addition, certain ethnic groups such as native Hawaiians and Israeli Jews have been observed to have a higher overall incidence than the general population. Testicular cancers are divided histologically into germ cell tumors, including seminomas, teratomas, embryonal carcinomas, and choriocarcinomas, and nongerm cell tumors including gonadoblastomas, Sertoli cell tumors, and Leydig cell adenomas. Germ cell tumors account for 90% to 95% of all testicular tumors, with seminomas comprising roughly 40% to 50% of this group. The primary risk factor for testicular cancer is a cryptorchid testis. This has been shown to confer an increased risk on both the affected and contralateral testes. Other potential risks include trauma, hormone exposure, and mumps atrophy.[172] Extragonadal germ cell tumors are seen with an increased incidence in patients with Klinefelter's syndrome.[173]

Familial Clustering

Case reports as far back as 1930 described multiple cases of testicular cancer within a single family.[174] These reports led to the obvious question of whether a heritable component in the development of testicular cancer existed. The first investigators to explore this question set about to ascertain if familial cases in fact existed and, if so, at what frequency. In 1985 the National Cancer Institute published data collected from 1976 to 1981. Two-hundred sixty-nine men with a histological diagnosis of testicular cancer of various types were compared to a control group of 259 men who had other nontesticular malignancies and who were stratified for age and race. Six cases of a first-degree relative diagnosed with testicular cancer within the patient group and only one case in the control group were identified. This was an incidence of 2.2% in the testicular cancer patient group. From this the authors calculated an RR of 5.9 (CI = 0.7 to 49.1) for contracting testicular cancer with the history of an affected first-degree relative.[175]

Two European studies, one from Britain and the other from Sweden, were later conducted in an attempt to confirm and expand upon the findings of these studies. Drawing data from the UK cancer registry, the first group found 42 families with 2 or more affected members and nearly 800 random other men with confirmed testicular cancer.[176] The family history of the 800 men was compared against 800 age-matched controls. Twelve affected first-degree relatives in the patient group were identified (an incidence of 1.5%) vs only 2 in the control group. Relative risks were calculated for affected brothers and fathers, demonstrating that an affected brother conferred a twofold higher RR of contracting testicular cancer than an affected father (8.0 vs 4.0). The authors then looked at the 42 families with 2 or more diagnosed members. These "familial cases" were compared against the men who had no family history of testicular cancer. The histologies for both groups were

divided into either pure seminomas or nonseminomas. The age of onset of pure seminomas in the familial group was found to be 32.5 vs 35.5 years in the sporadic group. The age of onset of nonseminomas was 26 in the familial group vs 28.5 in the sporadic group. Overall the median age of onset was 29 vs 32.5. The age differences between pure seminomas as well as for the overall group were statistically significant ($P < 0.05$ and $P < 0.01$, respectively).

The Swedish group took a similar approach to the British study and identified 797 Norwegian and 178 Swedish men diagnosed with testicular cancer.[177] An overall incidence of an affected first-degree relative was found in 2.8% of cases. Their analysis was expanded to include second- and third-degree relatives as well and found an incidence of 4.8%. The authors then calculated the RRs of developing cancer in the presence of an affected brother or father. A nearly twofold higher increase in risk with an affected brother (10.2 vs 4.3) was observed, and seminomas developed at a significantly younger age in familial cases vs sporadic cases (32.9 vs 37.6 years). Finally, the incidence of bilaterality in the familial and sporadic cases was significantly higher in patients with a positive family history (9.8% vs 2.8%).

These studies confirmed the earlier findings from the National Cancer Institute. Although the incidence of an affected first-degree family member varied somewhat (1.5% to 2.8%), all three clearly demonstrated an increased relative risk for men with an affected brother or father. In addition, the European studies agreed that familial cases arise at a significantly younger age than sporadic cases. The compilation of this epidemiological data provided conclusive evidence to support a heritable component accounting for a significant percentage of testicular cancer cases.

Inheritance Patterns

A British group set forth to quantify this heritable component in terms of gene frequency and penetrance. Cases of testicular cancer were categorized as genetically predisposed bilateral cases, genetically predisposed unilateral cases, and sporadic unilateral cases. Drawing from published data on the overall incidence of disease, the incidence of familial disease, the incidence of bilateral cases, and the expected incidence of bilaterality from chance alone, 33% of all testicular cancers were estimated to be genetically predisposed with a penetrance of 0.45.[178] Further, a homozygous autosomal-recessive gene with an overall frequency of 5% that could account for that genetic predisposition was proposed, implying that 10% of all men would be carriers of the testicular cancer susceptibility gene.

A Scandinavian study 2 years later attempted to confirm the results of Nicholson et al. These authors looked at 978 men with testicular cancer and found 30 of them with an affected first-degree relative. A segregation analysis was performed to look for a model of inheritance that would best fit the observed pattern of distribution of disease within the families. Of autosomal-recessive, autosomal-dominant, sporadic, and polygenic models, an autosomal recessive model best fit their data.

A genetic frequency of 3.8% was calculated, implying a 7.6% allele carrier rate and a penetrance of 0.43. Consequently, 25% of testicular cancer cases in men less than 35 years would be attributed to this allele.[179] While the estimations of gene frequency and penetrance varied slightly between the two studies, both provided evidence for an autosomal recessive, moderately penetrant allele, accounting for between 25% to 33% of testicular cancer cases.

Potential Alleles

For the past several years, efforts have been made to identify candidate regions for a testicular cancer susceptibility gene. Two major studies have been completed in England and Scandinavia searching for autosomal genes. The first of these, by Leahy et al., examined 35 families with 2 or 3 affected brothers per family.[180] Linkage analysis between sibling pairs using 220 autosomal microsatellite markers spaced throughout the genome was performed, identifying 6 significant candidate regions for a testicular cancer susceptibility gene. These were located on chromosomes *1p, 4p, 4q, 5q, 14q,* and *18q*. A low threshold for significance ($P < 0.05$) in identifying these candidate regions was set to not overlook the true region, acknowledging that this introduced a high likelihood of false positives. The most significant of these regions was on *4q*. Genes of interest on *4q* that lie near the candidate region include the α-fetoprotein gene, which is known to be overexpressed in many types of testicular cancer, and the gene *KIT*, a proto-oncogene.

The second study was actually a report from the International Testicular Cancer Linkage Consortium.[181] These authors used the analysis of the 35 families from Leahy et al. as well as an additional 15 other families. This data was combined with 54 more families, also with two or more affected members, identified through the Consortium. This second group of families was similarly screened for linkages using multiple microsatellite markers. Combining the results from the two groups failed to confirm any of the regions identified by Leahy et al. Analysis of the combined data did yield regions on chromosomes 3, 5, 12, and 18, which were significant for candidate loci. Nevertheless, the authors acknowledged that none of these regions provided convincing evidence for a testicular cancer predisposition gene.

Because examination of the autosomal genome had provided little conclusive evidence for a testicular cancer gene, a group of investigators recently examined the X chromosome for potential linkages. Because it had been previously shown that an affected brother carried a twofold higher relative risk of contracting the disease vs an affected father, the investigators hypothesized that an X-linked inheritance could be involved. Using families from the Consortium, linkage analysis on patients for possible X-linked transmission was performed. A significant candidate region at *Xq27* was designated *TGCT1*.[182] Stronger evidence for linkage at this location was found in the subset of families with at least one member with bilateral tumors. To date, only one gene, *FMR1*, has been identified at this locus. *FMR1* is known

to be involved in fragile X syndrome, which does not include an increased incidence of testicular cancer. The authors hypothesized that the presence of an extra copy of *TGCT1* in Klinefelter's syndrome may account for the increased incidence of extragonadal germ cell tumors seen in that population.

Chromosome 12

In 1982, Atkin and Baker first reported an anomaly noticed while analyzing the chromosomes of 10 seminomas, 1 malignant teratoma, and 1 combined tumor. Each tumor contained a 12p isochromosome (i12p). This isochromosome essentially consisted of two chromosome 12 short arms. The authors hypothesized that i12p was involved in tumorigenesis through amplification of the 12p genome.[183] Later studies confirmed the observation of Atkins and Baker when 80% of testicular germ cell tumors were found to contain i12p.[184] In addition, the majority of the remaining 20% of tumors without i12p were found to have other translocations and rearrangements, which led to an amplification of 12p.[185,186] These findings provided strong evidence for a gene integral to the development of testicular cancer located on chromosome 12p. This gene or genes have not been isolated to date, and the role of 12p in testicular tumor genesis remains unclear. Some evidence does exist, though, that 12p may be required for invasive growth rather than the initiation of testicular tumors. Mostert et al. used florescent in situ hybridization to identify specifically amplified regions of 12p. *12p11.2–p12.1* amplification was found in tumors both with i12p and 12p translocation or rearrangements. Of interest also was the observation that no amplification existed in intratesticular germ cell neoplasia.[187] Drawing from this observation, Rosenberg et al. compared intratubular germ cell neoplasia samples and tumor samples for overrepresentation of 12p sequences. Amplification of 12p was found in 0 of 11 intratubular germ cell neoplasia samples and 16 of 17 tumor samples. The authors hypothesized that 12p was required for invasive growth of tumors cells, possibly by suppressing apoptosis.[188]

Conclusion

In summary, there is strong evidence that an affected first-degree relative, in particular a brother, confers an increased relative risk of contracting testicular cancer. The pattern of transmission appears consistent with an autosomal-recessive, moderately penetrant allele, accounting for about one quarter of all cases. Efforts to isolate this allele have so far been unsuccessful. A recurrent and consistent cytogenetic finding has been observed in testicular germ cell tumors—i12p. The role of 12p is unclear, but it appears to be involved with progression and maintenance of disease rather than its transmission or initiation.

Clinical Implications

The therapeutic implications of these findings again herald the implications for screening and early detection of testicular tumors. Clearly, an individual with a family history of testicular cancer, in particular in a first-degree relative, should be more cognizant of meticulous self-

examination and consider physician screening. Currently, there are no specific alleles or genes to screen affected families, but research continues in this area. The role of 12p is an exciting avenue for potential treatments for germ cell tumors. Once the specific gene or genes involved are isolated, their protein products and functions can be ascertained. This will provide invaluable information for the development of targeted antitumor therapies.

Conclusions

Clearly, significant progress has been made in beginning to identify specific genetic susceptibilities for urologic malignancies. The identification of specific genes that are responsible for or contribute to the development of urologic malignancies holds the same potential clinical implications for the diagnosis and treatment of all cancers. One of the earliest applications that is already being utilized is the identification of tumors of unknown origin through the molecular subclassification of histological tumor types. The driving hope is that through characterization of the molecular events involved in the development and progression of cancer, early diagnosis for high-risk populations may be feasible. Early detection will theoretically allow utilization of the most effective, least toxic treatment strategy for an individual patient. Even more futuristic will be tailoring of chemopreventive agents for high-risk populations and design of effective treatments for specific tumor types in affected individuals utilizing small molecules or potentially corrective gene therapy strategies.

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10

Genetics of Multiple Endocrine Neoplasia

Derrick J. Beech

Multiple endocrine neoplasia (MEN) are inherited syndromes comprised of several endocrine disorders. There are two general categories of MEN, types 1 and 2. *MEN1* is phenotypically characterized by parathyroid gland hyperplasia, pancreatic islet cell tumors, and tumors of the anterior pituitary gland.[1] There are two different subcategories of *MEN2*; *MEN2A* is characterized by medullary thyroid cancer (MTC), pheochromocytoma, and parathyroid hyperplasia; *MEN2B* is comprised of MTC and adrenal pheochromocytoma along with mucosal neuromas, bony abnormalities, marfanoid habitus, and ganglioneuromas of the intestines, puffy lips, and corneal nerve hypertrophy. Familial MTC has similar features to MEN both clinically and genetically and will be included in this chapter.

MEN1 and *MEN2* with their associated germline mutations are the prototypical syndromes for which early identification of gene mutations and resection of the appropriate end organ will positively impact on survival of individuals with this disease. DNA testing can lead to the identification of individuals with disease in the occult state. For example, patients with an identified *RET* mutation and *MEN2* and familial medullary thyroid cancer syndrome might have a total thyroidectomy performed based on this identified genetic defect. Surgical intervention will remove the occult disease and significantly impact on the patient's survival. Specific genetic alterations are associated with the phenotypic characteristics in MEN.

Unique to MEN is the predictable development of specific clinical endocrine diseases based on identifiable genetic defects. *MEN1* and *MEN2* have identifiable genetic alterations that translate into the development of well-characterized phenotype expression. Similar genetic alterations are seen with familial MTC. This chapter will outline the genetic defects in MEN and suggest approaches to genetic testing. In kindreds with *MEN2*, evidence-based approaches to the identification of subjects with *RET* mutations and recommendations for prophylactic operative resection will be explained.

Multiple Endocrine Neoplasia Type 1

MEN1 typically becomes clinically evident by the third and fourth decade of life for women and men, respectively.[2] The majority of patients will have more than one organ system involved, and one fifth of patients will manifest adenomas in three endocrine sites. The most common manifestation of *MEN1* is primary hyperparathyroidism and associated hypercalcemia resulting from parathyroid gland hyperplasia. The second most common organ site to be involved in *MEN1* is the pancreas. Adenomas of the pituitary gland, adrenal gland, and thyroid may also occur, as can gastric, bronchial, or thymic carcinoid tumors.[3]

Hypercalcemia, kidney stones, peptic ulcer disease, hypoglycemia, headache, changes in visual fields, hypopituitarism, acromegaly, galactorrhea, amenorrhea, or Cushing's syndrome are potential clinical findings in patients with *MEN1*.[4–6] Although *MEN1* is a syndrome in which many of the neoplasms are benign, patients have a significantly reduced life expectancy with a 50% mortality rate by age 50.[7,8]

Primary hyperparathyroidism is the most consistent clinical endocrinopathy in *MEN1*, affecting 88% to 97% of individuals.[9] Parathyroid gland hyperplasia is the pathologic entity responsible for the elevated serum calcium and parathyroid hormone levels. Patients are typically identified using serological screening for primary hyperparathyroidism (elevated serum calcium and parathyroid hormone levels). Pancreatic islet cell tumors may on occasion become clinically evident before parathyroid disease.

Pancreatic islet cell tumors are the second most common endocrinopathy associated with *MEN1*. Pancreatic peptide-secreting tumors are the most common type, occurring in 80% to 100% of pancreatic endocrine tumors in *MEN1*.[10] These lesions are typically malignant and are the most common cause of death in patients with *MEN1*.[8]

Werner's syndrome, *MEN1*, is an autosomal-dominant inherited disorder resulting from a defect in chromosome 11 (q13 locus).[11] This syndrome is characterized by parathyroid hyperplasia, pituitary tumors, and pancreatic islet cell tumors.[12] The peak incidence of disease is in the third and fourth decade of life for men and women, respectively. A significant number of patients will have adenomas of more than one gland. Patients may also develop foregut or midgut carcinoid tumors. Patients may develop symptoms from hyperparathyroidism such as nephrolithiasis or peptic ulcer disease. Hypopituitarism, acromegoly, galactorrhea, or amenorrhea can on occasion be seen.

The most common finding in patients with *MEN1* is primary hyperparathyroidism, which occurs in up to 97% of patients.[9] Multiglandular hyperplasia is the etiology of primary hyperparathyroidism. Treatment of the parathyroid disease in *MEN1* requires resection of three and one half or all four parathyroid glands. If all four glands are removed then autotransplantation is done in the forearm musculature.

The most common cause of death in *MEN1* is malignant pancreatic islet cell tumors.[8] Pancreatic peptic-producing tumors are the most common, representing 80% to 100% of islet cell malignancies in *MEN1*.[10] In addition to pancreatic peptide-producing tumors, gastri-

nomas, insulinomas (20%), glucagonomas (3%), and vasoactive intestinal peptide (VIPoma) (1%) may also occur.[13]

There has been no clinical study demonstrating improved survival using operative resection in patients with *MEN1*. Resection of nongastrinoma pancreatic islet cell tumors in *MEN1* is beneficial, with a significantly large percentage of patients having biochemical disease cure.

Pituitary adenomas may become symptomatic due to local encroachment on the optic nerve producing visual field defects or headache. These tumors occur in 54% to 80% of patients with *MEN1*.[13] The most common pituitary tumor seen with *MEN1* is prolactinoma (41% to 76% of lesions).[14] Clinically, prolactinomas are manifested by absence of penile erection in men and galactorrhea in women. Patients may also demonstrate acromegaly (due to growth hormone) or Cushing's syndrome (due to adrenocorticotropic hormone). Management of prolactinomas can include dopamine receptor agonist. Transphenoidal resection of the pituitary tumor is also used to treat anterior pituitary lesions in these patients. Patients with *MEN1* may also develop other adrenal abnormalities (27% to 36%), thyroid adenomas (5% to 30%), along with lipomas, angiofibromas, or collagenomas.

The cornerstone to surgical management of *MEN1* is operative resection of all four parathyroid glands with placement of grafted parathyroid tissue in the nondominant forearm muscles. Operative management of parathyroid hyperplasia is usually performed prior to the surgical treatment of gastrinomas because the control of hypercalcemia can minimize adverse sequelae from pancreatic islet cell tumors.

MEN1 Genetics

The consistent feature in patients with *MEN1* is the development of hyperparathyroidism. Hyperparathyroidism is usually due to parathyroid hyperplasia and occurs in 90% of people with this syndrome. Clinical manifestations of hyperparathyroidism are usually evident by the second or third decade of life.

MEN1 is classically described as a syndrome consisting of the "three ps"—pancreatic islet cell tumors, parathyroid hyperplasia, and pituitary tumors. Universally, the pituitary tumors occur in the anterior pituitary gland. *MEN1* can also on occasion include carcinoid tumors or lipomas.

MEN1 has variable penetrance and is inherited as an autosomal-dominant disorder. The gene responsible for MEN1 is *Menin*.[15] *Menin* is a tumor suppressor gene occurring on the long arm of chromosome 11.[16] *MEN2A* and *MEN2B* are both inherited as autosomal-dominant conditions associated with the *RET* oncogene.[17] This gene is located at the pericentromeric region of chromosome 10.[18]

Menin is associated with a 2- to 8-kilobase mRNA that encodes for a protein product consisting of 610 amino acids.[19] Several different types of mutations can occur, resulting in the phenotypic *MEN1* syndrome. Missense mutations, frameshifts, and nonsense mutations can occur, resulting in the disruption of the wild-type gene.[20] The major-

ity of mutations result in the truncation of the C-terminal portion of the *Menin* protein.[21]

Menin is thought to act by binding Jun D, a transcription regulation factor, thus inhibiting Jun D-activated transcription.[22] Wild-type *Menin* is thought to maintain the integrity of DNA; thus when mutated, *Menin* and *MEN1* are characterized by chromosomal instability.

Multiple Endocrine Neoplasia Type 2

MEN2A and *MEN2B* result from unidentifiable mutations in the *RET* protooncogene. The most consistent phenotypic feature of both is the development of MTC. This malignancy develops from the parafollicular cells of the thyroid gland.

The frequency of associated endocrinopathies in *MEN2A* varies with pheochromocytomas and primary hyperparathyroidism occurring in 17% to 60% of patients.[22] Sipple initially described the high rate of bilateral pheochromocytomas in patients with thyroid malignancies in 1961.[17] This was later found to be associated with hyperparathyroidism and designated "MEN2" (later called *MEN2A*).

Patients with *MEN2A* may also develop cutaneous lichen amyloidosis, which is characterized by brown-pigmented macular amyloidosis with a cluster of papules in the interscapular area.[23] Patients may also have clinical manifestation of Hirschprung's disease in association with the other endocrinopathies of *MEN2A*. As with the non–MEN-associated Hirschprung's disease, functional obstruction and megacolon can develop from the absence of autonomic ganglion cells in the parasympathetic plexus of the distal colon.

As with *MEN2A*, patients with *MEN2B* develop a virulent form of MTC. Medullary thyroid cancer develops in these patients at a relatively early age and is rarely curable. Patients with *MEN2B* develop neural gangliomas mainly of the gastrointestinal tract, including the lips and tongue. These gangliomas may also develop on the conjunctiva. Skeletal abnormalities may also develop in this syndrome. Unlike *MEN2A*, hyperparathyroidism is not seen in patients with *MEN2B*.

MEN2 Genetics

The *RET* oncogene was localized to the pericentromeric portion of chromosome 10 in 1987. *RET* was further mapped to the long arm of chromosome 10, and ultimately this mutation was linked to *MEN2*.[24,25]

There are numerous missense mutations identified in *MEN2A*. The majority of mutations result in nonconservative changes in cysteine residue. Many of these mutations result in an activated *RET* protein product with increased tyrosine kinase activity.[26]

The *RET* gene has greater than 20 exons with 5 mRNA species.[27] The *RET* gene products consist of a cysteine-rich extracellular domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase catalytic domain. The gene products of *RET* are typically expressed in select cell types in normal individuals, including thyroid C cells and cells of the adrenal medulla and brain.[28]

Functionally, wild-type *RET* activation results in dimerization and phosphorylation of the intracellular tyrosine kinase domain. When *MEN2A* mutations are present in the *RET* proto-oncogene, the protein is constitutively activated. This is not the case for protein products of *RET* mutations in *MEN2B*. In *MEN2B* constitutive dimerization and receptor activation does not occur; rather, transformation results from changes in substrate specificity.

Screening and Surgical Intervention for *MEN2A*

The development of MTC in individuals with *MEN2A* has a nearly 100% penetrance. The majority of patients develop this malignancy before age 30; hence, individuals with *RET* mutations are considered for prophylactic thyroidectomy. Several studies support operative intervention based on the presence of *RET* mutations rather than the confirmatory study of elevated plasma calcitonin or stimulated calcitonin levels. Wells and associates evaluated 13 asymptomatic *RET* mutation carriers treated with thyroidectomy.[29] The total cohort screened included 132 subjects from kindreds affected by *MEN2A*. Forty-eight subjects had an *MEN2A* diagnosis. Fifty-eight subjects had a 50% risk of developing *MEN2A* but had no clinical evidence of disease. Of these 58 subjects, sequence-based direct mutation DNA analysis identified 21 subjects with inherited *RET* mutation. Stimulated calcitonin levels were assessed in all 21 subjects. Nine of the 21 subjects evaluated showed elevated levels of stimulated calcitonin. Thirteen members of this cohort (6 with normal stimulated calcitonin and 7 with elevated stimulated calcitonin levels) underwent total thyroidectomy, lymph node dissection, and parathyroid autotransplantation. All of the patients with elevated stimulated calcitonin levels (7/7) had microscopic evidence of MTC on the resected specimen. Medullary thyroid cancer was evident in half (3/6) of the patients with normal stimulated calcitonin levels.

This evolution was the impetus for a later report evaluating the utility of preventive thyroidectomies in subjects with *RET* mutations. Fourteen children had *RET* mutations evident on genetic testing and underwent subsequent thyroidectomies. Long-term follow-up demonstrated no recurrence of disease. These data support the frequent therapeutic use of total thyroidectomy in subjects with a family history of *MEN2* and identifiable *RET* mutations.

Familial Medullary Thyroid Cancer

Familial MTC is characterized by MTC in the absence of other endocrinopathies.[29] Although a frequent component of *MEN2*, MTC can occur in the absence of other clinical manifestations of MEN and is histologically similar to MTC in patients with sporadic disease or *MEN2A* or *MEN2B*. Medullary thyroid cancer is a neuroendocrine malignancy of the calcitonin-secreting parafollicular cells (C cells). Typical features of familial MTC are that of bilaterality and multifocal lesions. Sporadic

forms of MTC are usually unilateral, unlike the familial counterpart. Medullary thyroid cancer seen in patients with familial MTC is usually less virulent than MTC associated with *MEN2*.[30]

Familial MTC is an autosomal-dominant condition associated with a germline mutation of the *RET* proto-oncogene. Familial MTC represents approximately 10% of all types of MTC.[31] Clinical presentation of patients with familial MTC is similar to that of MTC found as a component of *MEN2*. Medullary thyroid cancer is the most consistent endocrinopathy seen with *MEN2A* and *MEN2B*. Patients may present with symptoms of neck fullness or shortness of breath. Stimulated or random calcitonin levels may be elevated.

Genetic evaluation of screening for familial MTC or MTC as a component of *MEN2A* or *MEN2B* hinges on the detection of missense mutations of the *RET* proto-oncogene.[32] *RET* mutations are typically detected in the peripheral leukocytes.[33] The usual technique for *RET* mutation analysis involves the use of reverse transcriptase (RT) polymerase chain reaction (PCR) to detect point mutations in exons 10 and 11 (codons 609, 611, 618, 620, and 634) in the case of familial MTC and *MEN2A*. For *MEN2B*, point mutations occur in codon 918. The identification of the specific codon for the point mutation allows evaluation of kindreds with similar areas of defects and, in the case of a codon 918 mutation, categorizing the syndrome as *MEN2B*.[34]

The presence of an *RET* mutation has a 100% penetrance, with all patients ultimately developing MTC.[35] If there is an *RET* mutation, patients should have basal calcitonin levels evaluated. These patients should also undergo stimulated plasma calcitonin level evaluation. Basal calcitonin levels of greater than 1 mg/mL usually signify the presence of clinically apparent or occult MTC.[36] Patients with normal basal levels of plasma calcitonin undergo stimulated plasma calcitonin assessment. Both calcium and pentigastrin are used in this provocative test. In the case of stimulated calcium, it is given as a bolus or infusion. Bolus calcium is given in the form of calcium glucuronate (2 mg/kg over 1 minute) followed by plasma calcitonin assessment. When calcium is used as an infusion in the stimulation test, it is usually given at doses of 15 mg/kg over 4 hours. Pentigastrin is used in the calcitonin-stimulating test at doses of 0.5-mg/kg intravenous bolus.[37]

In patients with an identified *RET* mutation and elevated basal or stimulated calcitonin level, it is recommended that they undergo operative management. If *RET* mutations are found in a member of a known MEN kindred, then operative management is recommended regardless of basal or stimulated calcitonin levels. C-cell hyperplasia or MTC is universally discovered with these prophylactic resections.

Prior to the operative management of MTC in patients with *RET* mutations, it is critical to exclude the presence of pheochromocytomas.[38] Prior to surgery, patients should have urinary levels of epinephrine, norepinephrine, vanillylmandelic acid, and metanephrine evaluated. Localizing studies may include an abdominal computed tomography scan, magnetic resonance imaging, or scintigraphy using metaiodobenzyl guanidine.

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